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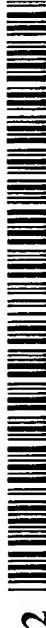
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(54) Title: CNGH0004 POLYPEPTIDES, ANTIBODIES, COMPOSITIONS, METHODS AND USES

(57) Abstract: The present invention relates to at least one novel CNGH0004 polypeptides, antibodies, including isolated nucleic acids that encode at least one CNGH0004 polypeptide or antibody, CNGH0004 vectors, host cells, transgenic animals or plants, and methods of making and using thereof, including therapeutic compositions, methods and devices.

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**CNGH0004 POLYPEPTIDES, ANTIBODIES,
COMPOSITIONS, METHODS AND USES****BACKGROUND OF THE INVENTION****FIELD OF THE INVENTION**

10 The present invention relates to at least one CNGH0004 polypeptide or fragment thereof, and antibodies and anti-idiotype antibodies specific therefore, as well as nucleic acids encoding such CNGH0004 polypeptides, fragments, antibodies, complementary nucleic acids, vectors, host cells, and methods of making and using thereof, including therapeutic formulations, administration and devices.

15 RELATED ART

Psoriasis is a genetic, multifactorial, chronic inflammatory skin disease, with a prevalence of 2.6% of the US population. The disease is characterized by pronounced hyperproliferation of keratinocytes, which results in rapid epidermal turnover and thickened, scaly, red plaques observed clinically. Other prominent histopathological features of the disease are alterations of cytokine production, fibroblast activation, vascular expansion, and leukocyte infiltration in the dermis and epidermis. Dysregulation in cytokine production from both activated cells in the dermis and the immune cells seems to play an important role in mediating the inflammatory events associated with psoriasis. To this end, a number of changes in gene and/or protein expression have been described previously in psoriasis and some of these genes and/or proteins have also been found to be associated 20 with other inflammatory diseases. These include proinflammatory cytokines such as IL-1 and TNF α , adhesion molecules such as intercellular adhesion molecule 1 (ICAM1) and vascular adhesion molecule 1 (VCAM1), chemokines, and defensins. Recently, gene expression microarray technology has been applied to profile gene expression patterns in normal versus psoriatic lesional skins on a more 25 inclusive scale and has provided new insights to the pathogenesis of psoriasis.

30 cDNA microarray technology provides a format for the simultaneous measurement of the expression level of thousands of genes in a single hybridization assay. It is also amenable to an automated, high-throughput format. More importantly, microarray technology can be used to discover new genes, quantify and analyze gene expression and assign functionality to genes with unknown function. With the complete sequencing of human genome, identification and cloning of new genes is 35 now accomplished rapidly. However, to understand whether these genes encode new proteins or to further identify function of these new proteins has not been advanced as rapidly. The impediment has become one of the main reasons for the use of high throughput cDNA microarray technology in a well-

- 5 designed experimental setting to discover novel protein-encoding genes or genes with novel function that may subsequently become potential therapeutic targets for a variety of human diseases.

Accordingly, there is a need to provide CNGH0004 polypeptides or antibodies or fragments that overcome one or more of these problems, as well as improvements over known polypeptides or antibodies or fragments thereof.

10

SUMMARY OF THE INVENTION

This invention discloses the discovery of a novel CNGH0004 gene and polypeptides through data analysis of the microarray gene expression profiling in psoriatic lesional skin biopsy samples obtained from infliximab (REMICADE®, an anti-TNF α monoclonal antibody approved to treat rheumatoid arthritis and Crohn's disease) treated versus placebo treated patients. The invention sets forth 15 sequences coding for a gene designated CNGH0004, and presents evidence for said gene the roles of a developmental and tissue remodeling regulator and as a tumor specific marker. Said sequences include nucleic acid sequences of full-length cDNA, open reading frames (ORFs), probes (e.g. for PCR), antisense, ribozymes, and vectors containing the sequences and the polypeptides encoded by them.

Compositions and methods for the therapy and diagnosis of, as non-limiting examples, 20 psoriasis, rheumatoid arthritis, Crohn's disease, asthma, and cancer, as well as other CNGH0004 related diseases and disorders, as described herein or as known in the art. Compositions may comprise one or more protein isoforms, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses CNGH0004 protein, or a T cell that is specific for cells expressing a polypeptide encoded by 25 the gene. Such compositions may be used, for example, for the prevention and treatment of diseases such as psoriasis, asthma, and brain-, colon-, skin- and/or breast cancer. Diagnostic and prognostic methods based on detecting CNGH0004 protein, or mRNA encoding such a protein, in a sample are also disclosed.

The present invention provides isolated CNGH0004 polypeptides and encoding nucleic acid, as 30 well as CNGH0004 human, primate, rodent, mammalian, chimeric, or human CNGH0004 polypeptides, antibodies, immunoglobulins, cleavage products and other specified portions and variants thereof, as well as CNGH0004 polypeptide or antibody compositions, encoding or complementary nucleic acids, vectors, host cells, compositions, formulations, devices, transgenic animals, transgenic plants, and methods of making and using thereof, as described and enabled herein, in combination with 35 what is known in the art.

The present invention also provides at least one isolated CNGH0004 antibody as described herein. An antibody according to the present invention can include any polypeptide or peptide

- 5 containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) (also termed the hypervariable region or HV) of a heavy or light chain variable region, or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, wherein the antibody can be incorporated into an antibody of the present
10 invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding specific CNGH0004 polypeptides or antibodies, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising at least one of said CNGH0004 polypeptide or antibody encoding or complementary nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such antibody nucleic acids, vectors and/or host cells.

- 20 At least one antibody of the invention binds at least one specified epitope specific to at least one CNGH0004 polypeptide, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of said polypeptide, which epitope is preferably comprised of at least 1-5 amino acids of at least one portion thereof, such as but not limited to, at least one functional, extracellular, soluble, hydrophilic, external
25 or cytoplasmic domain of said polypeptide, or any portion thereof.

The at least one antibody can optionally comprise at least one specified portion of at least one complementarity determining region (CDR) (e.g., CDR1, CDR2 or CDR3 of the heavy or light chain variable region) and optionally at least one constant or variable framework region or any portion thereof. The at least one antibody amino acid sequence can further optionally comprise at least one specified substitution, insertion or deletion as described herein or as known in the art.

- 30 The present invention also provides at least one isolated CNGH0004 polypeptide or antibody as described herein, wherein the antibody has at least one activity. An CNGH0004 polypeptide antibody can thus be screened for a corresponding activity according to known methods, such as but not limited to, at least one biological activity towards a CNGH0004 polypeptide or polypeptide related function.

35 The present invention further provides at least one CNGH0004 anti-idiotype antibody to at least one CNGH0004 antibody of the present invention. The anti-idiotype antibody includes any

5 polypeptide or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be
10 derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, and the like. The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding at least one CNGH0004 anti-idiotype antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said CNGH0004 anti-idiotype
15 antibody encoding nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such anti-idiotype antibody nucleic acids, vectors and/or host cells.

The present invention also provides at least one method for expressing at least one CNGH0004 polypeptide or antibody, or CNGH0004 anti-idiotype antibody, in a host cell, comprising culturing a
20 host cell as described herein under conditions wherein at least one CNGH0004 antibody is expressed in detectable and/or recoverable amounts.

The present invention also provides at least one composition comprising (a) an isolated CNGH0004 polypeptide or antibody encoding nucleic acid and/or polypeptide or antibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically
25 acceptable, such as but not limited to known carriers or diluents. The composition can optionally further comprise at least one further compound, polypeptide or composition.

The present invention further provides at least one CNGH0004 polypeptide or antibody method or composition, for administering a therapeutically effective amount to modulate or treat at least one CNGH0004 related condition in a cell, tissue, organ, animal or patient and/or, prior to,
30 subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery of a therapeutically or prophylactically effective amount of at least one CNGH0004 polypeptide or antibody, according to the present invention.

The present invention further provides at least one CNGH0004 polypeptide or antibody
35 method or composition, for diagnosing at least one CNGH0004 related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

5 The present invention also provides at least one composition, device and/or method of delivery for diagnosing of at least one CNGH0004 polypeptide or antibody, according to the present invention.

In another aspect, the present invention provides at least one isolated mammalian CNGH0004 polypeptide, comprising the amino acid sequences as part of SEQ ID NO:1.

Also provided is an isolated nucleic acid encoding at least one isolated mammalian
10 CNGH0004 polypeptide; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from prokaryotic or eukaryotic cells, or fusion cells thereof, e.g., but not limited to, mammalian, plant or insect, such as but not limited to, CHO, myeloma, or lymphoma cells, bacterial cells, yeast cells, silk worm cells, or any derivative, immortalized or transformed cell thereof. Also
15 provided is a method for producing at least one CNGH0004 polypeptide, comprising translating the polypeptide encoding nucleic acid under conditions *in vitro*, *in vivo* or *in situ*, such that the CNGH0004 polypeptide is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian CNGH0004 polypeptide and at least one pharmaceutically acceptable carrier or diluent. The composition can
20 optionally further comprise an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a
25 topical drug, a nutritional drug or the like, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a
30 stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is a method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one
35 isolated mammalian CNGH0004 polypeptide of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.0000001-500 mg/kilogram per: 1-24 hours, 1-7 days, 1-52 weeks, 1-24 months, 1-30 years (or any range or value

- 5 therein), of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administrating by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, 10 intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of an 15 anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise administering, prior, concurrently or after the (a) 20 contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, an anti-inflammatory, a non-steroid inflammatory drug (NTHE), an analgesic, anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an 25 immunization, an immunoglobulin, an immunosuppressive, a hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is at least one medical device, comprising at least one isolated mammalian CNGH0004 polypeptide of the invention, wherein the device is suitable to contacting or 30 administering the at least one CNGH0004 polypeptide by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, 35 intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use,

- 5 comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated mammalian CNGH0004 polypeptide of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial; intracelebellar, intracerebroventricular, intracolic, 10 intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian CNGH0004 15 polypeptide of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the polypeptide. Further provided in the present invention is at least one CNGH0004 polypeptide produced by the above method.

In another aspect the present invention provides at least one isolated mammalian CNGH0004 20 antibody, comprising at least one human CDR, wherein the antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:1.

The at least one antibody can optionally further comprise at least one characteristic selected from: (i) bind CNGH0004 with an affinity of at least one selected from at least 10^{-9} M, at least 10^{-10} M, at least 10^{-11} M, or at least 10^{-12} M; and/or (ii) substantially neutralizes at least one activity of at least 25 one CNGH0004 polypeptide. Also provided is an isolated nucleic acid encoding at least one isolated mammalian CNGH0004 antibody; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from prokaryotic or eukaryotic cells, or fusion cells thereof, e.g., but not limited to, mammalian, plant or insect, such as but not limited to, CHO, myeloma, or lymphoma 30 cells, bacterial cells, yeast cells, silk worm cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one CNGH0004 antibody, comprising translating the antibody encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the CNGH0004 antibody is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian CNGH0004 35 antibody and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug,

- 5 a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NTHE), an analgesic, anesthetic, a sedative, a local anesthetic, a
10 neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

15 The present invention further provides an anti-idiotype antibody or fragment that specifically binds at least one isolated mammalian CNGH0004 antibody of the present invention.

Also provided is a method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

- 20 (a) contacting or administering a composition comprising an effective amount of at least one isolated mammalian CNGH0004 antibody of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.0001-500 mg/kilogram of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administrating by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular,
25 intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

30 The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition

- 5 comprising an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, an anti-inflammatory, a non-steroid inflammatory drug (NTHE), an analgesic, anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a hormone, a
10 hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is at least one medical device, comprising at least one isolated mammalian CNGH0004 antibody of the invention, wherein the device is suitable to contacting or administering
15 the at least one CNGH0004 antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal,
20 intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated mammalian CNGH0004 antibody of the present invention. The article of manufacture
25 can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal,
30 intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian CNGH0004 antibody of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the antibody. Further provided in the
35 present invention is at least one CNGH0004 antibody produced by the above method.

The present invention further provides any invention described herein.

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DESCRIPTION OF THE INVENTION

The present invention provides isolated, recombinant and/or synthetic human CNGH0004 protein, as well as human, primate, rodent, mammalian, chimeric, humanized or CDR-grafted, antibodies and CNGH0004 anti-idiotype antibodies thereto, and compositions and encoding nucleic acid molecules comprising at least one polynucleotide encoding at least one CNGH0004 protein, 10 antibody or anti-idiotype antibody. The present invention further includes, but is not limited to, methods of making and using such nucleic acids and antibodies and anti-idiotype antibodies, including diagnostic and therapeutic compositions, methods and devices.

As used herein, an "CNGH0004 antibody," "CNGH0004 antibody," and the like include any polypeptide or peptide containing molecule that comprises at least a portion of an immunoglobulin 15 molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion, fragment or variant thereof, or at least one portion of an CNGH0004 receptor or binding polypeptide, which can be incorporated into a CNGH0004 antibody of the present invention.

20 Antibodies can include one or more of at least one CDR, at least one variable region, at least one constant region, at least one heavy chain (e.g., γ_1 , γ_2 , γ_3 , γ_4 , μ , α_1 , α_2 , δ , ϵ), at least one light chain (e.g., κ and λ), or any portion or fragment thereof, and can further comprise interchain and intrachain disulfide bonds, hinge regions, glycosylation sites that can be separated by a hinge region, as well as heavy chains and light chains. Light chains typically have a molecular weight of about 25Kd and 25 heavy chains typically range from 50K-77Kd. Light chains can exist in two distinct forms or isotypes, kappa (κ) and lambda (λ), which can combine with any of the heavy chain types. All light chains have at least one variable region and at least one constant region. The IgG antibody is considered a typical antibody structure and has two intrachain disulfide bonds in the light chain (one in variable region and one in the constant region), with four in the heavy chain, and such bond encompassing a peptide loop 30 of about 60-70 amino acids comprising a "domain" of about 110 amino acids in the chain. IgG antibodies can be characterized into four classes, IgG1, IgG2, IgG3 and IgG4. Each immunoglobulin class has a different set of functions. The following table summarizes the Physicochemical properties of each of the immunoglobulins classes and subclasses.

Property	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	SIgA	IgD	IgE
Heavy Chain	γ_1	γ_1	γ_1	γ_1	μ	α_1	α_2	α_1 / α_2	δ	ϵ
Mean Serum conc. (mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.05	0.03	0.00005

Sedimentation constant	7s	7s	7s	7s	19s	7s	7s	11s	7s	8s
Mol. Wt. (X 10 ³)	146	146	170	146	970	160	160	385	184	188
Half Life (days)	21	20	7	21	10	6	6	?	3	2
% intravascular distribution	45	45	45	45	80	42	42	Trac e	75	50
Carbohydrate (%)	2-3	2-3	2-3	2-3	12	7-11	7-11	7-11	9-14	12

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The following table summarizes non-limiting examples of antibody effector functions for human antibody classes and subclasses.

Effector function	IgG1	IgG2	IgG3	IgG4	IgM	IgA	IgD	IgE
Complement fixation	++	+	+++	-	+++	-	-	-
Placental transfer	+	+	+	+	-	-	-	-
Binding to Staph A	+++	+++	-	+++	-	-	-	-
Binding to Strep G	+++	+++	+++	+++	-	-	-	-

Accordingly, the type of antibody or fragment thereof can be selected for use according to the present invention based on the desired characteristics and functions that are desired for a particular therapeutic or diagnostic use, such as but not limited to serum half life, intravascular distribution, complement fixation, etc.

Antibody diversity is generated by at least 5 mechanisms, including (1) the use of multiple genes encoding parts of the antibody; (2) somatic mutation, e.g., primordial V gene mutation during B-cell ontogeny to produce different V genes in different B-cell clones; (3) somatic recombination, e.g., gene segments J1-Jn recombine to join the main part of the V-region gene during B-cell ontogeny; (4) gene conversion where sections of DNA from a number of pseudo V region can be copied into the V region to alter the DNA sequence; and (5) nucleotide addition, e.g., when V and J regions are cut, before joining, and extra nucleotides may be inserted to code for additional amino acids. Non-limiting examples include, but are not limited to, (i) the selection/recombination of V_K, J, and C_K regions from germ line to B-cell clones to generate kappa chains; (ii) selection/recombination of V_λ, J, and C_λ regions from germ line to B-cell clones to generate lambda chains; (iii) selection/recombination of V_H, D1-D30 and J_{H1}-J_{H6} genes to form a functional VDJ gene encoding a heavy chain variable region. The above mechanisms work in a coordinated fashion to generate antibody diversity and specificity.

The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian CNGH0004. For example, antibody fragments

- 5 capable of binding to CNGH0004 or portions thereof, including, but not limited to Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')₂ (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, et al., eds., Current Protocols in
10 Immunology, John Wiley & Sons, Inc., NY (1994-2001)).

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')₂ heavy chain portion can
15 be designed to include DNA sequences encoding the CH₁ domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous polypeptide using genetic engineering techniques.

As used herein, the term "human antibody" refers to an antibody in which substantially every part of the polypeptide (e.g., CDR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, (V_L, V_H))
20 is substantially non-immunogenic in humans, with only minor sequence changes or variations.

Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in
25 humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies.
30 For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two
35 different antigens. In the present case, one of the binding specificities is for at least one CNGH0004 polypeptide, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-

- 5 expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, *Nature* 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather
- 10 cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, US Patent Nos. 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, 4676980, WO 91/00360, WO 92/00373, EP 03089, Traunecker et al., *EMBO J.* 10:3655 (1991), Suresh et al., *Methods in Enzymology* 121:210 (1986), each entirely incorporated herein by reference.
- 15 Such antibodies optionally further affect a specific ligand, such as but not limited to where such antibody modulates, decreases, increases, antagonizes, agonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one CNGH0004 activity or binding, or with CNGH0004 receptor activity or binding, *in vitro*, *in situ* and/or *in vivo*. As a non-limiting example, a suitable CNGH0004 antibody, specified portion or variant of the present invention can bind at least one
- 20 CNGH0004, or specified portions, variants or domains thereof. A suitable CNGH0004 antibody, specified portion, or variant can also optionally affect at least one of CNGH0004 activity or function, such as but not limited to, RNA, DNA or polypeptide synthesis, CNGH0004 release, CNGH0004 receptor signaling, membrane CNGH0004 cleavage, CNGH0004 activity, CNGH0004 production and/or synthesis.
- 25 CNGH0004 antibodies (also termed CNGH0004 antibodies) useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to CNGH0004 and optionally and preferably having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low
- 30 immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in
- 35 less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double

- 5 antigen enzyme immunoassay) (Elliott *et al.*, *Lancet* 344:1125-1127 (1994), entirely incorporated herein by reference).

Utility

CNGH0004 protein is predicted to be an extracellular matrix protein. All CNGH0004 protein domains are characterized as extracellular domains. In addition to normal placenta and fetal tissue development, protein domains that constitute CNGH0004 are probably also involved in tissue remodeling of airway smooth muscle as well as psoriatic epithelium. Based on its domain structure, CNGH0004 may function through mediating adhesion via metal ion-dependent adhesion sites (MIDAS), or via modulating complement control related to immunological responses. As such, CNGH0004 is a potential therapeutic target for treatment of autoimmune or chronic inflammatory diseases including, but not limited to psoriasis or asthma, and different types of cancers.

The isolated nucleic acids of the present invention can be used for production of at least one CNGH0004 antibody or specified variant thereof, which can be used to measure or effect in a cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one CNGH0004 condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified CNGH0004 related condition.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one CNGH0004 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 µg/ml serum concentration per single, multiple, or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

All publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and

- 5 Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Polypeptide Science, John Wiley & Sons, NY, NY, (1997-2001).

Antibodies of the Present Invention.

- At least one CNGH0004 antibody of the present invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Polypeptide Science, John Wiley & Sons, NY, NY, (1997-2001), each entirely incorporated herein by reference.

Human antibodies that are specific for human CNGH0004 polypeptides or fragments thereof can be raised against an appropriate immunogenic antigen, such as isolated and/or CNGH0004 polypeptide or a portion thereof (including synthetic molecules, such as synthetic peptides). Other specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L.5, >243, P3X63Ag8.653, Sp2 SA3, Sp2 MA1, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV, MOLT4, DA-1, 25 JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144, NAMAIWA, NEURO 2A, or the like, or heteromylomas, fusion products thereof, or any cell or fusion cell derived therefrom, or any other suitable cell line as known in the art. See, e.g., www.atcc.org, www.lifetech.com., and the like, with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light 30 chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. See, e.g., Ausubel, 35 supra, and Colligan, Immunology, supra, chapter 2, entirely incorporated herein by reference.

Antibody producing cells can also be obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing heterologous or endogenous

- 5 nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).
- 10 Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or polypeptide library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite; Xoma, Berkeley, CA; Ixsys. See, e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; US 08/350260(5/12/94); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps); EP 614 989 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); US 20 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or polypeptides - US 5723323, 5763192, 5814476, 5817483, 5824514, 5976862, WO 86/05803, EP 590 689 (Ixsys, now Applied Molecular Evolution (AME), each entirely incorporated herein by reference) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., Microbiol. Immunol. 41:901-907 25 (1997); Sandhu et al., Crit. Rev. Biotechnol. 16:95-118 (1996); Eren et al., Immunol. 93:154-161 (1998), each entirely incorporated by reference as well as related patents and applications) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display (Hanes et al., Proc. Natl. Acad. Sci. USA, 94:4937-4942 (May 1997); Hanes et al., Proc. Natl. Acad. Sci. USA, 95:14130-14135 (Nov. 30 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (US pat. No. 5,627,052, Wen et al., J. Immunol. 17:887-892 (1987); Babcock et al., Proc. Natl. Acad. Sci. USA 93:7843-7848 (1996)); gel microdroplet and flow cytometry (Powell et al., Biotechnol. 8:333-337 (1990); One Cell Systems, Cambridge, MA; Gray et al., J. Imm. Meth. 182:155-163 (1995); Kenny et al., Bio/Technol. 13:787-790 (1995)); B-cell selection (Steenbakkers et al., 35 Molec. Biol. Reports 19:125-134 (1994); Jonak et al., Progress Biotech, Vol. 5, In Vitro Immunization in Hybridoma Technology, Borrebaeck, ed., Elsevier Science Publishers B.V., Amsterdam, Netherlands (1988)).

5 Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source which is non-human, e.g., but not limited to mouse, rat, rabbit, non-human primate or other mammal. These human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence. Known human Ig sequences are disclosed, e.g., www.ncbi.nlm.nih.gov/entrez/query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/; www.abcam.com/; www.antibodyresource.com/onlinecomp.html; www.public.iastate.edu/~pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html; www.whfreeman.com/immunology/CH05/kuby05.htm; www.library.thinkquest.org/12429/Immune/Antibody.html; www.hhmi.org/grants/lectures/1996/vlab/;

10 15 www.path.cam.ac.uk/~mrc7/mikeimages.html; www.antibodyresource.com/; mcb.harvard.edu/BioLinks/Immunology.html; www.immunologylink.com/; pathbox.wustl.edu/~hcenter/index.html; www.biotech.ufl.edu/~hcl/; www.pebio.com/pa/340913/340913.html; www.nal.usda.gov/awic/pubs/antibody/; www.m.ehime-u.ac.jp/~yasuhito/Elisa.html; www.biodesign.com/table.asp;

20 25 www.icnet.uk/axp/facs/davies/links.html; www.biotech.ufl.edu/~fccl/protocol.html; www.isac-net.org/sites_geo.html; axim1.imt.uni-marburg.de/~rek/AEPStart.html; baserv.uci.kun.nl/~jraats/links1.html; www.recab.uni-hd.de/immuno.bme.nwu.edu/; www.mrc-cpe.cam.ac.uk/imt-doc/public/INTRO.html; www.ibt.unam.mx/vir/V_mice.html; imgt.cnusc.fr:8104/; www.biochem.ucl.ac.uk/~martin/abs/index.html; antibody.bath.ac.uk/;

30 35 abgen.cvm.tamu.edu/lab/wwwabgen.html; www.unizh.ch/~honegger/AHOseminar/Slide01.html; www.cryst.bbk.ac.uk/~ubcg07s/; www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm; www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html; www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html; www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html; www.jerini.de/fr_products.htm; www.patents.ibm.com/ibm.html. Kabat et al., Sequences of Polypeptides of Immunological Interest, U.S. Dept. Health (1983), each entirely incorporated herein by reference.

Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with human or other amino acids. Antibodies can also optionally be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, humanized antibodies can be

5 optionally prepared by a process of analysis of the parental sequences and various conceptual
humanized products using three-dimensional models of the parental and humanized sequences. Three-
dimensional immunoglobulin models are commonly available and are familiar to those skilled in the
art. Computer programs are available which illustrate and display probable three-dimensional
conformational structures of selected candidate immunoglobulin sequences. Inspection of these
10 displays permits analysis of the likely role of the residues in the functioning of the candidate
immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate
immunoglobulin to bind its antigen. In this way, framework residues can be selected and combined
from the consensus and import sequences so that the desired antibody characteristic, such as increased
affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most
15 substantially involved in influencing antigen binding. Humanization or engineering of antibodies of
the present invention can be performed using any known method, such as but not limited to those
described in, Winter (Jones et al., Nature 321:522 (1986); Riechmann et al., Nature 332:323 (1988);
Verhoeyen et al., Science 239:1534 (1988)), Sims et al., J. Immunol. 151: 2296 (1993); Chothia and
Lesk, J. Mol. Biol. 196:901 (1987), Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta
20 et al., J. Immunol. 151:2623 (1993), US patent Nos: 5723323, 5976862, 5824514, 5817483, 5814476,
5763192, 5723323, 5,766886, 5714352, 6204023, 6180370, 5693762, 5530101, 5585089, 5225539;
4816567, PCT/: US98/16280, US96/18978, US91/09630, US91/05939, US94/01234, GB89/01334,
GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, EP 229246, each entirely
incorporated herein by reference, included references cited therein.

25 The CNGH0004 antibody can also be optionally generated by immunization of a transgenic
animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire
of human antibodies, as described herein and/or as known in the art. Cells that produce a human
CNGH0004 antibody can be isolated from such animals and immortalized using suitable methods, such
as the methods described herein and/or as known in the art.

30 Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens
can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos: 5,770,428, 5,569,825,
5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg *et al.*;
Jakobovits *et al.* WO 98/50433, Jakobovits *et al.* WO 98/24893, Lonberg *et al.* WO 98/24884, Lonberg
et al. WO 97/13852, Lonberg *et al.* WO 94/25585, Kucherlapate *et al.* WO 96/34096, Kucherlapate *et*
35 *al.* EP 0463 151 B1, Kucherlapate *et al.* EP 0710 719 A1, Surani *et al.* US. Pat. No. 5,545,807,
Bruggemann *et al.* WO 90/04036, Bruggemann *et al.* EP 0438 474 B1, Lonberg *et al.* EP 0814 259 A2,
Lonberg *et al.* GB 2 272 440 A, Lonberg *et al.* *Nature* 368:856-859 (1994), Taylor *et al.*, *Int. Immunol.*

- 5 6(4)579-591 (1994), Green *et al.*, *Nature Genetics* 7:13-21 (1994), Mendez *et al.*, *Nature Genetics* 15:146-156 (1997), Taylor *et al.*, *Nucleic Acids Research* 20(23):6287-6295 (1992), Tuailon *et al.*, *Proc Natl Acad Sci USA* 90(8)3720-3724 (1993), Lonberg *et al.*, *Int Rev Immunol* 13(1):65-93 (1995) and Fishwald *et al.*, *Nat Biotechnol* 14(7):845-851 (1996), which are each entirely incorporated herein by reference). Generally, these mice comprise at least one transgene comprising DNA from at least
10 one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement. The endogenous immunoglobulin loci in such mice can be disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by endogenous genes.

Screening antibodies for specific binding to similar polypeptides or fragments can be conveniently achieved using peptide display libraries. This method involves the screening of large collections of peptides for individual members having the desired function or structure. antibody screening of peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5000 or more amino acids in length, frequently from 5-100 amino acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical synthetic methods for generating peptide libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such methods are described in PCT Patent Publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278. Other systems for generating libraries of peptides have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and
15 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from such suppliers as Invitrogen (Carlsbad, CA), and Cambridge antibody Technologies (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030, 5518889, 5534621, 5656730,
20 5763733, 5767260, 5856456, assigned to Enzon; 5223409, 5403484, 5571698, 5837500, assigned to Dyax, 5427908, 5580717, assigned to Affymax; 5885793, assigned to Cambridge antibody Technologies;
25 5750373, assigned to Genentech, 5618920, 5595898, 5576195, 5698435, 5693493, 5698417, assigned to Xoma, Colligan, *supra*; Ausubel, *supra*; or Sambrook, *supra*, each of the above patents and publications entirely incorporated herein by reference.

Antibodies of the present invention can also be prepared using at least one CNGH0004 antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, US patent nos. 5,827,690; 5,849,992; 4,873,316;

- 5 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

Antibodies of the present invention can additionally be prepared using at least one CNGH0004 antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant polypeptides have been successfully used to provide large amounts of recombinant polypeptides, e.g., using an inducible promoter. See, e.g., Cramer et al., *Curr. Top. Microbiol. Immunol.* 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian polypeptides at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., *Adv. Exp. Med. Biol.* 464:127-147 (1999) and references cited therein. Antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., *Plant Mol. Biol.* 38:101-109 (1998) and reference cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to known methods. See also, e.g., Fischer et al., *Biotechnol. Appl. Biochem.* 30:99-108 (Oct., 1999); Ma et al., *Trends Biotechnol.* 13:522-7 (1995); Ma et al., *Plant Physiol.* 109:341-6 (1995); Whitelam et al., *Biochem. Soc. Trans.* 22:940-944 (1994); and references cited therein. Each of the above references is entirely incorporated herein by reference.

The antibodies of the invention can bind human CNGH0004 with a wide range of affinities (K_D). In a preferred embodiment, at least one human mAb of the present invention can optionally bind human CNGH0004 with high affinity. For example, a human mAb can bind human CNGH0004 with a K_D equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) $\times 10^{-7}$, 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} , 10^{-12} , 10^{-13} or any range or value therein.

The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, et al., "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., K_D , K_a , K_d) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

Nucleic Acid Molecules

5 Using the information provided herein, such as the nucleotide sequences encoding at least 70-100% of the contiguous amino acids of at least one of SEQ ID NO:1, specified fragments, variants or consensus sequences thereof, or a deposited vector comprising at least one of these sequences, a nucleic acid molecule of the present invention encoding at least one CNGH0004 antibody can be obtained using methods described herein or as known in the art, such as but not limited to SEQ ID
10 NO:2.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any combination thereof. Any portion of
15 at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

Isolated nucleic acid molecules of the present invention can include nucleic acid molecules comprising an open reading frame (ORF), optionally with one or more introns, e.g., but not limited to, at least one specified portion of at least one CDR, as CDR1, CDR2 and/or CDR3 of at least one heavy
20 chain or light chain; nucleic acid molecules comprising the coding sequence for an CNGH0004 antibody or variable region; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one CNGH0004 antibody as described herein and/or as known in the art. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to
25 generate such degenerate nucleic acid variants that code for specific CNGH0004 antibodies of the present invention. See, e.g., Ausubel, et al., *supra*, and such nucleic acid variants are included in the present invention. Non-limiting examples of isolated nucleic acid molecules of the present invention include the CDR sequences corresponding to non-limiting examples of a nucleic acid encoding, respectively, HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, LC CDR3, HC variable region
30 and LC variable region.

As indicated herein, nucleic acid molecules of the present invention which comprise a nucleic acid encoding a CNGH0004 antibody can include, but are not limited to, those encoding the amino acid sequence of an antibody fragment, by itself; the coding sequence for the entire antibody or a portion thereof; the coding sequence for an antibody, fragment or portion, as well as additional sequences, such
35 as the coding sequence of at least one signal leader or fusion peptide, intron, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals (for example - ribosome binding and

- 5 stability of mRNA); an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding an antibody can be fused to a marker sequence, such as a sequence encoding a peptide that facilitates purification of the fused antibody comprising an antibody fragment or portion.

10 **Polynucleotides Which Selectively Hybridize to a Polynucleotide as Described Herein**

The present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides of the present invention can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

Preferably, the cDNA library comprises at least 80% full-length sequences, preferably at least 85% or 90% full-length sequences, and more preferably at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify orthologous or paralogous sequences.

30 Optionally, polynucleotides of this invention will encode at least a portion of an antibody encoded by the polynucleotides described herein. The polynucleotides of this invention embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding an antibody of the present invention. See, e.g., Ausubel, *supra*; Colligan, *supra*, each entirely incorporated herein by reference.

Construction of Nucleic Acids

The isolated nucleic acids of the present invention can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, or combinations thereof, as well-known in the art.

35 The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the polypeptides of

- 5 the present invention. The nucleic acid of the present invention - excluding the coding sequence - is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

Additional sequences can be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the 10 introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Recombinant Methods for Constructing Nucleic Acids

The isolated nucleic acid compositions of this invention, such as RNA, cDNA, genomic DNA, or any combination thereof, can be obtained from biological sources using any number of cloning 15 methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes that selectively hybridize, under stringent conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. The isolation of RNA, and construction of cDNA and genomic libraries, is well known to those of ordinary skill in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Nucleic Acid Screening and Isolation Methods

A cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide of the present invention, such as those disclosed herein. Probes can be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different organisms. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be 25 employed in the assay; and either the hybridization or the wash medium can be stringent. As the conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by one or more of temperature, ionic strength, pH and the presence of a partially denaturing solvent such as formamide. For example, the stringency of hybridization is conveniently varied by 30 changing the polarity of the reactant solution through, for example, manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of complementarity will optimally be 100%, or 70-100%, or any range or value therein. However, it should be understood that minor sequence variations in the probes and primers 35 can be compensated for by reducing the stringency of the hybridization and/or wash medium.

5 Methods of amplification of RNA or DNA are well known in the art and can be used according to the present invention without undue experimentation, based on the teaching and guidance presented herein.

Known methods of DNA or RNA amplification include, but are not limited to, polymerase chain reaction (PCR) and related amplification processes (see, e.g., U.S. Patent Nos. 4,683,195, 10 4,683,202, 4,800,159, 4,965,188, to Mullis, et al.; 4,795,699 and 4,921,794 to Tabor, et al; 5,142,033 to Innis; 5,122,464 to Wilson, et al.; 5,091,310 to Innis; 5,066,584 to Gyllensten, et al; 4,889,818 to Gelfand, et al; 4,994,370 to Silver, et al; 4,766,067 to Biswas; 4,656,134 to Ringold) and RNA mediated amplification that uses anti-sense RNA to the target sequence as a template for double-stranded DNA synthesis (U.S. Patent No. 5,130,238 to Malek, et al, with the tradename NASBA), the entire contents of which references are incorporated herein by reference. (See, e.g., Ausubel, *supra*; or 15 Sambrook, *supra*.)

For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and other in vitro amplification methods can also be useful, for example, to clone nucleic acid sequences that code for polypeptides to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through in vitro amplification methods are found in Berger, *supra*, Sambrook, *supra*, and Ausubel, *supra*, as well as Mullis, et al., U.S. Patent No. 4,683,202 (1987); and Innis, et al., *PCR Protocols A Guide to Methods and Applications*, Eds., 20 Academic Press Inc., San Diego, CA (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). Additionally, e.g., the T4 gene 32 polypeptide (Boehringer Mannheim) can be used to improve yield of long PCR products.

Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids of the present invention can also be prepared by direct chemical synthesis by known methods (see, e.g., Ausubel, et al., *supra*). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer sequences can be obtained by the ligation of shorter 35 sequences.

Recombinant Expression Cassettes

5 The present invention further provides recombinant expression cassettes comprising a nucleic acid of the present invention. A nucleic acid sequence of the present invention, for example a cDNA or a genomic sequence encoding an antibody of the present invention, can be used to construct a recombinant expression cassette that can be introduced into at least one desired host cell. A recombinant expression cassette will typically comprise a polynucleotide of the present invention operably linked to
10 transcriptional initiation regulatory sequences that will direct the transcription of the polynucleotide in the intended host cell. Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the nucleic acids of the present invention.

15 In some embodiments, isolated nucleic acids that serve as promoter, enhancer, or other elements can be introduced in the appropriate position (upstream, downstream or in intron) of a non-heterologous form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide of the present invention. For example, endogenous promoters can be altered *in vivo* or *in vitro* by mutation, deletion and/or substitution.

Vectors And Host Cells

20 The present invention also relates to vectors that include isolated nucleic acid molecules of the present invention, host cells that are genetically engineered with the recombinant vectors, and the production of at least one CNGH0004 antibody by recombinant techniques, as is well known in the art. See, e.g., Sambrook, et al., *supra*; Ausubel, et al., *supra*, each entirely incorporated herein by reference.

25 The polynucleotides can optionally be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it can be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

30 The DNA insert should be operatively linked to an appropriate promoter. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (e.g., UAA, UGA or UAG) appropriately positioned at the end of the mRNA to be translated, with UAA and UAG preferred for mammalian or eukaryotic cell expression.

35 Expression vectors will preferably but optionally include at least one selectable marker. Such markers include, e.g., but not limited to, methotrexate (MTX), dihydrofolate reductase (DHFR, US Pat.Nos. 4,399,216; 4,634,665; 4,656,134; 4,956,288; 5,149,636; 5,179,017, ampicillin, neomycin (G418), mycophenolic acid, or glutamine synthetase (GS, US Pat.Nos. 5,122,464; 5,770,359;

5 5,827,739) resistance for eukaryotic cell culture, and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria or prokaryotics (the above patents are entirely incorporated hereby by reference). Appropriate culture mediums and conditions for the above-described host cells are known in the art. Suitable vectors will be readily apparent to the skilled artisan. Introduction of a vector construct into a host cell can be effected by calcium phosphate transfection, DEAE-dextran
10 mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other known methods. Such methods are described in the art, such as Sambrook, supra, Chapters 1-4 and 16-18; Ausubel, supra, Chapters 1, 9, 13, 15, 16.

At least one antibody of the present invention can be expressed in a modified form, such as a fusion polypeptide, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of an antibody to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to an antibody of the present invention to facilitate purification. Such regions can be removed prior to final preparation of an antibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, supra, Chapters 16, 17 and 18.

Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a polypeptide of the present invention.

Alternatively, nucleic acids of the present invention can be expressed in a host cell by turning on 25 (by manipulation) in a host cell that contains endogenous DNA encoding an antibody of the present invention. Such methods are well known in the art, e.g., as described in US patent Nos. 5,580,734, 5,641,670, 5,733,746, and 5,733,761, entirely incorporated herein by reference.

Illustrative of cell cultures useful for the production of the antibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of monolayers of 30 cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated polypeptides have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, Cos-7 cells, CHO cells, hep G2 cells, P3X63Ag8.653, SP2/0-Ag14, 293 cells, HeLa cells and the like, which are 35 readily available from, for example, American Type Culture Collection, Manassas, Va (www.atcc.org). Preferred host cells include cells of lymphoid origin such as myeloma and lymphoma cells.

Particularly preferred host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and

- 5 SP2/0-Ag14 cells (ATCC Accession Number CRL-1851). In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or a SP2/0-Ag14 cell.

Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839), an HSV tk promoter, a pgk 10 (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., *supra*; Sambrook, et al., *supra*. Other cells useful for production of nucleic acids or polypeptides of the present invention are known and/or available, 15 for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (www.atcc.org) or other known or commercial sources.

When eukaryotic host cells are employed, polyadenylation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenylation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript can 20 also be included. An example of a splicing sequence is the VP1 intron from SV40 (Sprague, et al., *J. Virol.* 45:773-781 (1983)). Additionally, gene sequences to control replication in the host cell can be incorporated into the vector, as known in the art.

Purification of a CNGH0004 Polypeptide or Antibody

A CNGH0004 polypeptide or antibody can be recovered and purified from recombinant cell 25 cultures by well-known methods including, but not limited to, polypeptide A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, *Current Protocols in* 30 *Immunology*, or *Current Protocols in Polypeptide Science*, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10, each entirely incorporated herein by reference.

CNGH0004 polypeptides and antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. 35 Depending upon the host employed in a recombinant production procedure, the polypeptide or antibody of the present invention can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, *supra*,

- 5 Sections 17.37-17.42; Ausubel, *supra*, Chapters 10, 12, 13, 16, 18 and 20, Colligan, *Protein Science*, *supra*, Chapters 12-14, all entirely incorporated herein by reference.

CNGH0004 Polypeptides and Antibodies

The isolated polypeptides and antibodies of the present invention comprise at least one polypeptide and/or antibody amino acid sequence disclosed or described herein encoded by any suitable 10 polynucleotide, or any at least one isolated or prepared polypeptide antibody. Preferably, the at least one polypeptide has at least one CNGH0004 activity and the at least one antibody binds human CNGH0004 and, thereby partially or substantially modulates at least one structural or biological activity of at least one CNGH0004 polypeptide.

As used herein, the term "CNGH0004 polypeptide" refers to a polypeptide as described herein 15 that has at least one CNGH0004-dependent activity, such as 5-10000%, of the activity of a known or other CNGH0004 polypeptide or active portion thereof, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, or 1000% or more, depending on the assay. The capacity of a CNGH0004 polypeptide to have at least one CNGH0004-dependent activity is preferably assessed by at least one suitable 20 CNGH0004 polypeptide or receptor assay, as described herein and/or as known in the art.

As used herein, the term "neutralizing antibody" refers to an antibody that can inhibit at least one CNGH0004-dependent activity by about 5-1020%, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, or 1000% or more depending on the assay. The capacity of a CNGH0004 antibody to 25 inhibit an CNGH0004-dependent activity is preferably assessed by at least one suitable CNGH0004 polypeptide or receptor assay, as described herein and/or as known in the art. An antibody of the invention can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. Antibodies of this type can be 30 prepared by employing a transgenic mouse or other transgenic non-human mammal comprising at least one human light chain (e.g., combination of V, D and J regions) or heavy chain (e.g., $\gamma 1$, $\gamma 2$, $\gamma 3$, $\gamma 4$, $\mu 1$, $\alpha 1$, $\alpha 2$, δ , ϵ) transgenes as described herein and/or as known in the art. In another embodiment, the human CNGH0004 human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

At least one antibody of the invention binds at least one specified epitope specific to at least 35 one CNGH0004 polypeptide, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of the polypeptide, which epitope can optionally comprise at least one portion of at least one extracellular,

- 5 soluble, hydrophilic, external or cytoplasmic portion of the polypeptide. The at least one specified epitope can comprise any combination of at least one amino acid sequence of at least 1-3 amino acids to the entire specified portion of contiguous amino acids of the SEQ ID NO:1.

The at least one antibody of the present invention can preferably comprise at least one antigen-binding region that comprises at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one heavy chain variable region and/or at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one light chain variable region. In a particular embodiment, the polypeptide and antibody can have an antigen-binding region that comprises at least a portion of at least one heavy chain (HC) CDR (i.e., HC CDR1, HC CDR2 and/or HC CDR3) having the amino acid sequence of the corresponding HC CDRs 1, 2 and/or

10 3. In another particular embodiment, the antibody or antigen-binding portion or variant can have at least one antigen-binding region that comprises at least a portion of at least one light chain (LC) CDR (i.e., LC CDR1, LC CDR2 and/or LC CDR3). Such antibodies can be prepared by chemically joining together the various portions (e.g., CDRs, framework) of the antibody using conventional techniques, by preparing and expressing a (i.e., one or more) nucleic acid molecule that encodes the antibody using

15 conventional techniques of recombinant DNA technology or by using any other suitable method.

The CNGH0004 antibody can comprise at least one of a heavy or light chain variable region having a defined amino acid sequence. For example, in a preferred embodiment, the CNGH0004 antibody comprises at least one heavy chain variable region; and/or at least one light chain variable region. Antibodies that bind to human CNGH0004 and that comprise a defined heavy or light chain variable region can be prepared using suitable methods, such as phage display (Katsume, Y., et al., *Int J Mol. Med.*, 1(5):863-868 (1998)) or methods that employ transgenic animals, as known in the art and/or as described herein. For example, a transgenic mouse, comprising a functionally rearranged human immunoglobulin heavy chain transgene and a transgene comprising DNA from a human immunoglobulin light chain locus that can undergo functional rearrangement, can be immunized with

25 human CNGH0004 or a fragment thereof to elicit the production of antibodies. If desired, the antibody producing cells can be isolated and hybridomas or other immortalized antibody-producing cells can be prepared as described herein and/or as known in the art. Alternatively, the antibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

The invention also relates to antibodies, antigen-binding fragments, immunoglobulin chains and CDRs comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Preferably, such antibodies or antigen-binding fragments and antibodies comprising such chains or CDRs can bind human CNGH0004 with high affinity (e.g., K_D less than or

- 5 equal to about 10⁻⁹ M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising conservative amino acid substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g, charge, structure, polarity, hydrophobicity/ hydrophilicity) that are similar to those of the first amino acid.
- 10 Conservative substitutions include replacement of one amino acid by another within the following groups: lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.
- 15 **Amino Acid Codes**
The amino acids that make up CNGH0004 polypeptides or antibodies of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three letter code, name, or three nucleotide codon(s) as is well understood in the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc., New York, 1994):
- 20

SINGLE LETTER CODE	THREE LETTER CODE	NAME	THREE NUCLEOTIDE CODON(S)
A	Ala	Alanine	GCA, GCC, GCG, GCU
C	Cys	Cysteine	UGC, UGU
D	Asp	Aspartic acid	GAC, GAU
E	Glu	Glutamic acid	GAA, GAG
F	Phe	Phenylalanine	UUC, UUU
G	Gly	Glycine	GGA, GGC, GGG, GGU
H	His	Histidine	CAC, CAU
I	Ile	Isoleucine	AUA, AUC, AUU
K	Lys	Lysine	AAA, AAG
L	Leu	Leucine	UUA, UUG, CUA, CUC, CUG, CUU
M	Met	Methionine	AUG
N	Asn	Asparagine	AAC, AAU
P	Pro	Proline	CCA, CCC, CCG, CCU
Q	Gln	Glutamine	CAA, CAG
R	Arg	Arginine	AGA, AGG, CGA, CGC, CGG, CGU
S	Ser	Serine	AGC, AGU, UCA, UCC, UCG, UCU
T	Thr	Threonine	ACA, ACC, ACG, ACU
V	Val	Valine	GUU, GUC, GUG, GUU
W	Trp	Tryptophan	UGG

Y	Tyr	Tyrosine	UAC, UAU
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An CNGH0004 antibody of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein.

Of course, the number of amino acid substitutions a skilled artisan would make depends on 10 many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for any given CNGH0004 antibody, fragment or variant will not be more than 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, such as 1-30 or any range or value therein, as specified herein.

Amino acids in an CNGH0004 antibody of the present invention that are essential for function 15 can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, *supra*, Chapters 8, 15; Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to at least one CNGH0004 neutralizing activity. Sites that are critical for antibody binding can also be 20 identified by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., *J. Mol. Biol.* 224:899-904 (1992) and de Vos, et al., *Science* 255:306-312 (1992)).

CNGH0004 polypeptides of the present invention can include, but are not limited to, at least one portion, sequence or combination selected from 3-100 to all of the contiguous amino acids of at 25 least one of SEQ ID NO:1, such as but not limited to, 1-82, 83-259, 259-377, 378-433, 434-438, 438-493, 498-559, 1631-1685, 1690-1743, 1789-1842, 2021-2078, 2083-2141, 2146-2199, 2204-2259, 2264-2318, 2323-2376, 2381-2435, 2440-2493, 2498-2551, 2556-2608, 2660-2712, 2717-2770, 2775-2828, 2833-2886, 2891-2944, 2949-3002, 3007-3059, 3064-3117, 3122-3176, 3181-3236, 3241-3294, 3299-3352, 3357-3411, 3416-3468, 1231-1267, 1269-1305, 1307-1343, 1345-1381, 1383-1419, 1748-30 1784, 3468-3499, 3504-3531, 3536-3563, 1431-1623, 643-722, 561-642, 1196-1229, 727-787, 1847-1900, 1963-2016, 1905-1958, 999-1036, 1041-1106, 1108-1160, 1-41, or 305-360 of SEQ ID NO:1.

Non-limiting CDRs or portions of CNGH0004 polypeptides or antibodies of the invention that can enhance or maintain at least one of the listed activities include, but are not limited to, any of the above polypeptides, further comprising at least one mutation corresponding to at least one substitution 35 selected from the group consisting of at least one of S249L, V507I, C842W, E980G, Y1063C, K1416Q, D1442V, A1810E.

5 An CNGH0004 polypeptide can further optionally comprise a polypeptide of at least one of 70-100% of the contiguous amino acids of at least one of SEQ ID NO:1 or any variant thereof.

In one embodiment, the amino acid sequence of a CNGH0004 polypeptide or antibody has about 70-100% identity (e.g., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the amino acid sequence 10 of the corresponding chain of at least one of SEQ ID NO:1. Preferably, 70-100% amino acid identity (i.e., 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) is determined using a suitable computer algorithm, as known in the art.

The polypeptides and antibodies of the present invention, or specified variants thereof, can 15 comprise any number of contiguous amino acid residues from an antibody of the present invention, wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in a CNGH0004 polypeptide or antibody. Optionally, this subsequence of 20 contiguous amino acids is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 or more amino acids in length, or any range or value 25 therein. Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, or 5.

As those of skill will appreciate, the present invention includes at least one biologically active 30 polypeptide or antibody of the present invention. Biologically active polypeptides or antibodies have a specific activity at least 20%, 30%, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, or 95%-1000% of that of the native (non-synthetic), endogenous or related 35 and known polypeptide or antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity, are well known to those of skill in the art.

In another aspect, the invention relates to CNGH0004 polypeptides or antibodies of the 40 invention, as described herein, which are modified by the covalent attachment of a moiety. Such modification can produce a CNGH0004 polypeptide or antibody with improved pharmacokinetic properties (e.g., increased *in vivo* serum half-life). The organic moiety can be a linear or branched 45 hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrrolidone, and the fatty acid or fatty acid 50 ester group can comprise from about eight to about forty carbon atoms.

The modified polypeptides and antibodies of the invention can comprise one or more organic 55 moieties that are covalently bonded, directly or indirectly, to the antibody or polypeptide. Each

- 5 organic moiety that is bonded to the polypeptide or antibody of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, a CNGH0004 antibody
10 or polypeptide modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies or polypeptides of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine,
15 polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrrolidone. Preferably, the hydrophilic polymer that modifies the polypeptide or antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example PEG₅₀₀₀ and PEG_{20,000}, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted
20 with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.
- 25 Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C₁₂, laurate), n-tetradecanoate (C₁₄, myristate), n-octadecanoate (C₁₈, stearate), n-eicosanoate (C₂₀, arachidate), n-docosanoate (C₂₂, behenate), n-triacontanoate (C₃₀), n-tetracontanoate (C₄₀), *cis*-Δ9-octadecanoate (C₁₈, oleate), all *cis*-
30 Δ5,8,11,14-eicosatetraenoate (C₂₀, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.
- The modified human polypeptides and antibodies can be prepared using suitable methods, such
35 as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that

5 can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acryloyl, pyridyl disulfides; 5-thiol-2-nitrobenzoic acid thiol
10 (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic
15 group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C₁-C₁₂ group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, -(CH₂)₃-NH-(CH₂)₆-NH-, -(CH₂)₂-NH- and -CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH-NH-. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g.,
20 mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an
25 activated maleimido derivative of the fatty acid. (See, for example, Thompson, *et al.*, WO 92/16221 the entire teachings of which are incorporated herein by reference.)

Modified polypeptides or antibodies of the invention can be produced by reacting the polypeptide or antibody with a modifying agent. For example, the organic moieties can be bonded to the antibody or polypeptide in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified CNGH0004 polypeptides or antibodies can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of the polypeptide and antibody. The reduced polypeptide and antibody can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified polypeptides and antibodies comprising an organic moiety that is bonded to specific sites of an antibody of the present invention
30 can be prepared using suitable methods, such as reverse proteolysis (Fisch *et al.*, *Bioconjugate Chem.*, 3:147-153 (1992); Werlen *et al.*, *Bioconjugate Chem.*, 5:411-417 (1994); Kumaran *et al.*, *Polypeptide Sci.* 6(10):2233-2241 (1997); Itoh *et al.*, *Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas *et al.*,

- 5 *Biotechnol. Bioeng.*, 56(4):456-463 (1997)), and the methods described in Hermanson, G. T.,
Bioconjugate Techniques, Academic Press: San Diego, CA (1996).

ANTI-IDIOTYPE ANTIBODIES TO ANTI-CNGH0004 ANTIBODY COMPOSITIONS

In addition to monoclonal or chimeric CNGH0004 antibodies, the present invention is also directed to an idiotypic (Id) antibody specific for such antibodies of the invention. An anti-Id antibody is an antibody that recognizes unique determinants generally associated with the antigen-binding region of another antibody. The Id can be prepared by immunizing an animal of the same species and genetic type (e.g. mouse strain) as the source of the Id antibody with the antibody or a CDR containing region thereof. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody and produce an anti-Id antibody. The anti-Id antibody may 10 also be used as an "immunogen" to induce an immune response in yet another animal, producing a 15 so-called anti-Id antibody.

CNGH0004 POLYPEPTIDE AND ANTIBODY COMPOSITIONS

The present invention also provides at least one CNGH0004 antibody or polypeptide 20 composition comprising at least one, at least two, at least three, at least four, at least five, or at least 6-50, or any range or value therein, CNGH0004 antibodies or polypeptides thereof, as described herein. Such compositions can comprise 0.00001-99.9999 percent by weight, volume, concentration, molarity, or molality as liquid, gas, or dry solutions, mixtures, suspension, emulsions or colloids, as known in the art or as described herein, on any range or value therein, such as but not limited to 0.00001, 0.00003, 25 0.00005, 0.00009, 0.0001, 0.0003, 0.0005, 0.0009, 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4., 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 30 99.6, 99.7, 99.8, 99.9 %. Such compositions of the present invention thus include but are not limited to 0.00001-100 mg/ml and/or 0.00001-100 mg/g.

The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, 35 a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. Such drugs are well known in the art, including

- 5 formulations, indications, dosing and administration for each presented herein (see., e.g., Nursing 2001
Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's
Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ;
Pharmacotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely
incorporated herein by reference).
- 10 The anti-infective drug can be at least one selected from amebicides or at least one
antiprotozoals, anthelmintics, antifungals, antimalarials, antituberculotics or at least one antileprotics,
aminoglycosides, penicillins, cephalosporins, tetracyclines, sulfonamides, fluoroquinolones, antivirals,
macrolide anti-infectives, miscellaneous anti-infectives. The CV drug can be at least one selected from
inotropics, antiarrhythmics, antianginals, antihypertensives, antilipemics, miscellaneous cardiovascular
15 drugs. The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected
from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opioid analgesics,
sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous
system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can
be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics
20 (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular
blockers. The respiratory tract drug can be at least one selected from antihistamines, bronchodilators,
expectorants or at least one antitussives, miscellaneous respiratory drugs. The GI tract drug can be at
least one selected from antacids or at least one adsorbents or at least one antiflatulents, digestive
enzymes or at least one gallstone solubilizers, antidiarrheals, laxatives, antiemetics, antiulcer drugs.
- 25 The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic
steroids, estrogens or at least one progestins, gonadotropins, antidiabetic drugs or at least one glucagon,
thyroid hormones, thyroid hormone antagonists, pituitary hormones, parathyroid-like drugs. The drug
for fluid and electrolyte balance can be at least one selected from diuretics, electrolytes or at least one
replacement solutions, acidifiers or at least one alkalinizers. The hematologic drug can be at least one
30 selected from hematinics, anticoagulants, blood derivatives, thrombolytic enzymes. The
antineoplastics can be at least one selected from alkylating drugs, antimetabolites, antibiotic
antineoplastics, antineoplastics that alter hormone balance, miscellaneous antineoplastics. The
immunomodulation drug can be at least one selected from immunosuppressants, vaccines or at least
one toxoids, antitoxins or at least one antivenins, immune serums, biological response modifiers. The
35 ophthalmic, otic, and nasal drugs can be at least one selected from ophthalmic anti-infectives,
ophthalmic anti-inflammatories, miotics, mydriatics, ophthalmic vasoconstrictors, miscellaneous
ophthalmics, otics, nasal drugs. The topical drug can be at least one selected from local anti-infectives,

5 scabicides or at least one pediculicides, topical corticosteroids. The nutritional drug can be at least one selected from vitamins, minerals, or calorics. See, e.g., contents of *Nursing 2001 Drug Handbook, supra.*

The at least one amebicide or antiprotozoal can be at least one selected from atovaquone, chloroquine hydrochloride, chloroquine phosphate, metronidazole, metronidazole hydrochloride, 10 pentamidine isethionate. The at least one anthelmintic can be at least one selected from mebendazole, pyrantel pamoate, thiabendazole. The at least one antifungal can be at least one selected from amphotericin B, amphotericin B cholesteryl sulfate complex, amphotericin B lipid complex, amphotericin B liposomal, fluconazole, flucytosine, griseofulvin microsize, griseofulvin ultramicrosize, itraconazole, ketoconazole, nystatin, terbinafine hydrochloride. The at least one 15 antimarial can be at least one selected from chloroquine hydrochloride, chloroquine phosphate, doxycycline, hydroxychloroquine sulfate, mefloquine hydrochloride, primaquine phosphate, pyrimethamine, pyrimethamine with sulfadoxine. The at least one antituberculotic or antileprotic can be at least one selected from clofazimine, cycloserine, dapsone, ethambutol hydrochloride, isoniazid, 20 pyrazinamide, rifabutin, rifampin, rifapentine, streptomycin sulfate. The at least one aminoglycoside can be at least one selected from amikacin sulfate, gentamicin sulfate, neomycin sulfate, streptomycin sulfate, tobramycin sulfate. The at least one penicillin can be at least one selected from amoxicillin/clavulanate potassium, amoxicillin trihydrate, ampicillin, ampicillin sodium, ampicillin trihydrate, ampicillin sodium/sulbactam sodium, cloxacillin sodium, dicloxacillin sodium, mezlocillin sodium, nafcillin sodium, oxacillin sodium, penicillin G benzathine, penicillin G potassium, penicillin 25 G procaine, penicillin G sodium, penicillin V potassium, piperacillin sodium, piperacillin sodium/tazobactam sodium, ticarcillin disodium, ticarcillin disodium/clavulanate potassium. The at least one cephalosporin can be at least one selected from at least one of cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, cefpodoxime proxetil, 30 cefprozil, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalexin hydrochloride, cephalexin monohydrate, cephadrine, loracarbef. The at least one tetracycline can be at least one selected from demeclocycline hydrochloride, doxycycline calcium, doxycycline hyolate, doxycycline hydrochloride, doxycycline monohydrate, minocycline hydrochloride, tetracycline hydrochloride. The at least one sulfonamide can be at least one selected 35 from co-trimoxazole, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfisoxazole acetyl. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin,

- 5 trovafloxacin mesylate. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one antiviral can be at least one selected from abacavir sulfate, acyclovir sodium, amantadine hydrochloride, amprenavir, cidofovir, delavirdine mesylate, didanosine, efavirenz, famciclovir, fomivirsen sodium, foscarnet sodium, ganciclovir, indinavir sulfate, lamivudine, lamivudine/zidovudine, nelfinavir mesylate, nevirapine, oseltamivir phosphate, ribavirin, rimantadine hydrochloride, ritonavir, saquinavir, saquinavir mesylate, stavudine, valacyclovir hydrochloride, zalcitabine, zanamivir, zidovudine. The at least one macroline anti-infective can be at least one selected from azithromycin, clarithromycin, dirithromycin, erythromycin base, erythromycin estolate, erythromycin ethylsuccinate, erythromycin lactobionate, erythromycin stearate. The at least one miscellaneous anti-infective can be at least one selected from aztreonam, bacitracin, chloramphenicol sodium succinate, clindamycin hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate, imipenem and cilastatin sodium, meropenem, nitrofurantoin macrocrystals, nitrofurantoin microcrystals, quinupristin/dalfopristin, spectinomycin hydrochloride, trimethoprim, vancomycin hydrochloride. (See, e.g., pp. 24-214 of
- 10 20 *Nursing 2001 Drug Handbook.*)

The at least one inotropic can be at least one selected from amrinone lactate, digoxin, milrinone lactate. The at least one antiarrhythmic can be at least one selected from adenosine, amiodarone hydrochloride, atropine sulfate, bretylium tosylate, diltiazem hydrochloride, disopyramide, disopyramide phosphate, esmolol hydrochloride, flecainide acetate, ibutilide fumarate, lidocaine hydrochloride, mexiletine hydrochloride, moricizine hydrochloride, phenytoin, phenytoin sodium, procainamide hydrochloride, propafenone hydrochloride, propranolol hydrochloride, quinidine bisulfate, quinidine gluconate, quinidine polygalacturonate, quinidine sulfate, sotalol, tocainide hydrochloride, verapamil hydrochloride. The at least one antianginal can be at least one selected from amlodipine besylate, amyl nitrite, bepridil hydrochloride, diltiazem hydrochloride, isosorbide dinitrate, isosorbide mononitrate, nadolol, nicardipine hydrochloride, nifedipine, nitroglycerin, propranolol hydrochloride, verapamil, verapamil hydrochloride. The at least one antihypertensive can be at least one selected from acebutolol hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol hydrochloride, bisoprolol fumarate, candesartan cilexetil, captopril, carteolol hydrochloride, carvedilol, clonidine, clonidine hydrochloride, diazoxide, diltiazem hydrochloride, doxazosin mesylate, enalaprilat, enalapril maleate, eprosartan mesylate, felodipine, fenoldopam mesylate, fosinopril sodium, guanabenz acetate, guanadrel sulfate, guanfacine hydrochloride, hydralazine hydrochloride, irbesartan, isradipine, labetalol hydrochloride, lisinopril, losartan potassium,

15 25 30 35

- 5 methyldopa, methyldopate hydrochloride, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril hydrochloride, nadolol, nicardipine hydrochloride, nifedipine, nisoldipine, nitroprusside sodium, penbutolol sulfate, perindopril erbumine, phentolamine mesylate, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, telmisartan, terazosin hydrochloride, timolol maleate, trandolapril, valsartan, verapamil hydrochloride. The at least one
10 antilipemic can be at least one selected from atorvastatin calcium, cerivastatin sodium, cholestyramine, colestipol hydrochloride, fenofibrate (micronized), fluvastatin sodium, gemfibrozil, lovastatin, niacin, pravastatin sodium; simvastatin. The at least one miscellaneous CV drug can be at least one selected from abciximab, alprostadil, arbutamine hydrochloride, cilostazol, clopidogrel bisulfate, dipyridamole, eptifibatide, midodrine hydrochloride, pentoxifylline, ticlopidine hydrochloride, tirofiban
15 hydrochloride. (See, e.g., pp. 215-336 of *Nursing 2001 Drug Handbook*.)

The at least one nonnarcotic analgesic or antipyretic can be at least one selected from acetaminophen, aspirin, choline magnesium trisalicylate, diflunisal, magnesium salicylate. The at least one nonsteroidal anti-inflammatory drug can be at least one selected from celecoxib, diclofenac potassium, diclofenac sodium, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, indomethacin sodium trihydrate, ketoprofen, ketorolac tromethamine, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, sulindac. The at least one narcotic or opioid analgesic can be at least one selected from alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulfate, fentanyl citrate, fentanyl transdermal system, fentanyl transmucosal, hydromorphone hydrochloride, meperidine hydrochloride, methadone hydrochloride, morphine hydrochloride, morphine sulfate, morphine tartrate, nalbuphine hydrochloride, oxycodone hydrochloride, oxycodone pectinate, oxymorphone hydrochloride, pentazocine hydrochloride, pentazocine hydrochloride and naloxone hydrochloride, pentazocine lactate, propoxyphene hydrochloride, propoxyphene napsylate, remifentanil hydrochloride, sufentanil citrate, tramadol hydrochloride. The at least one sedative-hypnotic can be at least one selected from chloral hydrate, estazolam, flurazepam hydrochloride, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, temazepam, triazolam, zaleplon, zolpidem tartrate. The at least one anticonvulsant can be at least one selected from acetazolamide sodium, carbamazepine, clonazepam, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximide, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate, valproate sodium, valproic acid. The at least one antidepressant can be at least one selected from amitriptyline hydrochloride, amitriptyline pamoate, amoxapine, bupropion hydrochloride, citalopram

5 hydrobromide, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, imipramine hydrochloride, imipramine pamoate, mirtazapine, nefazodone hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride, phenelzine sulfate, sertraline hydrochloride, tranylcypromine sulfate, trimipramine maleate, venlafaxine hydrochloride. The at least one antianxiety drug can be at least one selected from alprazolam, buspirone hydrochloride,
10 chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, doxepin hydrochloride, hydroxyzine embonate, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, mephobarbital, midazolam hydrochloride, oxazepam. The at least one antipsychotic drug can be at least one selected from chlorpromazine hydrochloride, clozapine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, haloperidol
15 lactate, loxapine hydrochloride, loxapine succinate, mesoridazine besylate, molindone hydrochloride, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine fumarate, risperidone, thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine hydrochloride. The at least one central nervous system stimulant can be at least one selected from amphetamine sulfate, caffeine, dextroamphetamine sulfate, doxapram hydrochloride, methamphetamine hydrochloride,
20 methylphenidate hydrochloride, modafinil, pemoline, phentermine hydrochloride. The at least one antiparkinsonian can be at least one selected from amantadine hydrochloride, benztrapine mesylate, biperiden hydrochloride, biperiden lactate, bromocriptine mesylate, carbidopa-levodopa, entacapone, levodopa, pergolide mesylate, pramipexole dihydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, trihexyphenidyl hydrochloride. The at least one miscellaneous central
25 nervous system drug can be at least one selected from bupropion hydrochloride, donepezil hydrochloride, droperidol, fluvoxamine maleate, lithium carbonate, lithium citrate, naratriptan hydrochloride, nicotine polacrilex, nicotine transdermal system, propofol, rizatriptan benzoate, sibutramine hydrochloride monohydrate, sumatriptan succinate, tacrine hydrochloride, zolmitriptan.
(See, e.g., pp. 337-530 of *Nursing 2001 Drug Handbook*.)

- 30 The at least one cholinergic (e.g., parasympathomimetic) can be at least one selected from bethanechol chloride, edrophonium chloride, neostigmine bromide, neostigmine methylsulfate, physostigmine salicylate, pyridostigmine bromide. The at least one anticholinergics can be at least one selected from atropine sulfate, dicyclomine hydrochloride, glycopyrrolate, hyoscyamine, hyoscyamine sulfate, propantheline bromide, scopolamine, scopolamine butylbromide, scopolamine hydrobromide.
35 The at least one adrenergics (sympathomimetics) can be at least one selected from dobutamine hydrochloride, dopamine hydrochloride, metaraminol bitartrate, norepinephrine bitartrate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate. The at least

- 5 one adrenergic blocker (sympatholytic) can be at least one selected from dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, propranolol hydrochloride. The at least one skeletal muscle relaxant can be at least one selected from baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine hydrochloride, dantrolene sodium, methocarbamol, tizanidine hydrochloride. The at least one neuromuscular blockers can be at least one selected from atracurium besylate, cisatracurium besylate,
- 10 doxacurium chloride, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rapacuronium bromide, rocuronium bromide, succinylcholine chloride, tubocurarine chloride, vecuronium bromide. (See, e.g., pp. 531-84 of *Nursing 2001 Drug Handbook*.)

The at least one antihistamine can be at least one selected from brompheniramine maleate, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, cyproheptadine

15 hydrochloride, diphenhydramine hydrochloride, fexofenadine hydrochloride, loratadine, promethazine hydrochloride, promethazine theoolate, triprolidine hydrochloride. The at least one bronchodilators can be at least one selected from albuterol, albuterol sulfate, aminophylline, atropine sulfate, ephedrine sulfate, epinephrine, epinephrine bitartrate, epinephrine hydrochloride, ipratropium bromide, isoproterenol, isoproterenol hydrochloride, isoproterenol sulfate, levalbuterol hydrochloride,

20 metaproterenol sulfate, oxtriphylline, pирbutерол acetate, salmeterol xinafoate, terbutaline sulfate, theophylline. The at least one expectorants or antitussives can be at least one selected from benzonatate, codeine phosphate, codeine sulfate, dextromethorphan hydrobromide, diphenhydramine hydrochloride, guaifenesin, hydromorphone hydrochloride. The at least one miscellaneous respiratory drug can be at least one selected from acetylcysteine, beclomethasone dipropionate, beractant,

25 budesonide, calfactant, cromolyn sodium, dornase alfa, epoprostenol sodium, flunisolide, fluticasone propionate, montelukast sodium, nedocromil sodium, palivizumab, triamcinolone acetonide, zafirlukast, zileuton. (See, e.g., pp. 585-642 of *Nursing 2001 Drug Handbook*.)

The at least one antacid, adsorbents, or antiflatulents can be at least one selected from aluminum carbonate, aluminum hydroxide, calcium carbonate, magaldrate, magnesium hydroxide, magnesium oxide, simethicone, sodium bicarbonate. The at least one digestive enzymes or gallstone solubilizers can be at least one selected from pancreatin, pancrelipase, ursodiol. The at least one antidiarrheal can be at least one selected from attapulgite, bismuth subsalicylate, calcium polycarbophil, diphenoxylate hydrochloride or atropine sulfate, loperamide, octreotide acetate, opium tincture, opium tincure (camphorated). The at least one laxative can be at least one selected from bisacodyl, calcium polycarbophil, cascara sagrada, cascara sagrada aromatic fluidextract, cascara sagrada fluidextract, castor oil, docusate calcium, docusate sodium, glycerin, lactulose, magnesium citrate, magnesium hydroxide, magnesium sulfate, methylcellulose, mineral oil, polyethylene glycol or

- 5 electrolyte solution, psyllium, senna, sodium phosphates. The at least one antiemetic can be at least one selected from chlorpromazine hydrochloride, dimenhydrinate, dolasetron mesylate, dronabinol, granisetron hydrochloride, meclizine hydrochloride, metoclopramide hydrochloride, ondansetron hydrochloride, perphenazine, prochlorperazine, prochlorperazine edisylate, prochlorperazine maleate, promethazine hydrochloride, scopolamine, thiethylperazine maleate, trimethobenzamide hydrochloride.

10 The at least one antiulcer drug can be at least one selected from cimetidine, cimetidine hydrochloride, famotidine, lansoprazole, misoprostol, nizatidine, omeprazole, rabeprozole sodium, rantidine bismuth citrate, ranitidine hydrochloride, sucralfate. (See, e.g., pp. 643-95 of *Nursing 2001 Drug Handbook*.)

The at least one corticosteroids can be at least one selected from betamethasone, betamethasone

- 15 acetate or betamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate. The at least one androgen or anabolic steroids can be at least one selected from danazol, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone transdermal system. The at least one estrogen or progestin can be at least one selected from esterified estrogens, estradiol, estradiol cypionate, estradiol/norethindrone acetate transdermal system, estradiol valerate, estrogens (conjugated), estropipate, ethinyl estradiol, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and levonorgestrel, ethinyl estradiol and norethindrone, ethinyl estradiol and norethindrone acetate, ethinyl estradiol and norgestimate, ethinyl estradiol and norgestrel, ethinyl estradiol and norethindrone and acetate and ferrous fumarate, levonorgestrel, medroxyprogesterone acetate, mestranol and norethindron, norethindrone, norethindrone acetate, norgestrel, progesterone.

20 The at least one gonadotropin can be at least one selected from ganirelix acetate, gonadoreline acetate, histrelin acetate, menotropins. The at least one antidiabetic or glucose can be at least one selected from acarbose, chlorpropamide, glimepiride, glipizide, glucagon, glyburide, insulins, metformin hydrochloride, miglitol, pioglitazone hydrochloride, repaglinide, rosiglitazone maleate, troglitazone. The at least one thyroid hormone can be at least one selected from levothyroxine sodium, liothyronine sodium, liotrix, thyroid. The at least one thyroid hormone antagonist can be at least one

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- 5 selected from methimazole, potassium iodide, potassium iodide (saturated solution), propylthiouracil, radioactive iodine (sodium iodide ^{131}I), strong iodine solution. The at least one pituitary hormone can be at least one selected from corticotropin, cosyntropin, desmopressin acetate, leuprolide acetate, repository corticotropin, somatrem, somatropin, vasopressin. The at least one parathyroid-like drug can be at least one selected from calcifediol, calcitonin (human), calcitonin (salmon), calcitriol,
10 dihydrotachysterol, etidronate disodium. (See, e.g., pp. 696-796 of *Nursing 2001 Drug Handbook*.)

The at least one diuretic can be at least one selected from acetazolamide, acetazolamide sodium, amiloride hydrochloride, bumetanide, chlorthalidone, ethacrylate sodium, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, mannitol, metolazone, spironolactone, torsemide, triamterene, urea. The at least one electrolyte or replacement solution can be at least one selected from
15 calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, calcium lactate, calcium phosphate (dibasic), calcium phosphate (tribasic), dextran (high-molecular-weight), dextran (low-molecular-weight), hetastarch, magnesium chloride, magnesium sulfate, potassium acetate, potassium bicarbonate, potassium chloride, potassium gluconate, Ringer's injection, Ringer's injection (lactated), sodium chloride. The at least one acidifier or alkalinizer can be at least one selected from sodium bicarbonate, sodium lactate, tromethamine.
20 (See, e.g., pp. 797-833 of *Nursing 2001 Drug Handbook*.)

The at least one hematinic can be at least one selected from ferrous fumarate, ferrous gluconate, ferrous sulfate, ferrous sulfate (dried), iron dextran, iron sorbitol, polysaccharide-iron complex, sodium ferric gluconate complex. The at least one anticoagulant can be at least one selected from ardeparin sodium, dalteparin sodium, danaparoid sodium, enoxaparin sodium, heparin calcium, heparin sodium, warfarin sodium. The at least one blood derivative can be at least one selected from albumin 5%, albumin 25%, antihemophilic factor, anti-inhibitor coagulant complex, antithrombin III (human), factor IX (human), factor IX complex, plasma protein fractions. The at least one thrombolytic enzyme can be at least one selected from alteplase, anistreplase, reteplase (recombinant),
30 streptokinase, urokinase. (See, e.g., pp. 834-66 of *Nursing 2001 Drug Handbook*.)

The at least one alkylating drug can be at least one selected from busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, lomustine, mechlorethamine hydrochloride, melphalan, melphalan hydrochloride, streptozocin, temozolomide, thioguanine. The at least one antimetabolite can be at least one selected from capecitabine, cladribine, cytarabine, floxuridine,
35 fludarabine phosphate, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, methotrexate sodium, thioguanine. The at least one antibiotic antineoplastic can be at least one selected from bleomycin sulfate, dactinomycin, daunorubicin citrate liposomal, daunorubicin hydrochloride, doxorubicin

- 5 hydrochloride, doxorubicin hydrochloride liposomal, epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, pentostatin, plicamycin, valrubicin. The at least one antineoplastics that alter hormone balance can be at least one selected from anastrozole, bicalutamide, estramustine phosphate sodium, exemestane, flutamide, goserelin acetate, letrozole, leuprolide acetate, megestrol acetate, nilutamide, tamoxifen citrate, testolactone, toremifene citrate. The at least one miscellaneous
10 antineoplastic can be at least one selected from asparaginase, bacillus Calmette-Guerin (BCG) (live intravesical), dacarbazine, docetaxel, etoposide, etoposide phosphate, gemcitabine hydrochloride, irinotecan hydrochloride, mitotane, mitoxantrone hydrochloride, paclitaxel, pegaspargase, porfimer sodium, procarbazine hydrochloride, rituximab, teniposide, topotecan hydrochloride, trastuzumab, tretinoin, vinblastine sulfate, vincristine sulfate, vinorelbine tartrate. (See, e.g., pp. 867-963 of *Nursing*
15 *2001 Drug Handbook.*)
The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, tacrolimus. The at least one vaccine or toxoid can be at least one selected from BCG vaccine, cholera vaccine, diphtheria and
20 tetanus toxoids (adsorbed), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, diphtheria and tetanus toxoids and whole-cell pertussis vaccine, *Haemophilus b* conjugate vaccines, hepatitis A vaccine (inactivated), hepatitis B vaccine (recombinant), influenza virus vaccine 1999-2000 trivalent types A & B (purified surface antigen), influenza virus vaccine 1999-2000 trivalent types A & B (subvirion or purified subvirion), influenza virus vaccine 1999-2000 trivalent types A & B (whole
25 virion), Japanese encephalitis virus vaccine (inactivated), Lyme disease vaccine (recombinant OspA), measles and mumps and rubella virus vaccine (live), measles and mumps and rubella virus vaccine (live attenuated), measles virus vaccine (live attenuated), meningococcal polysaccharide vaccine, mumps virus vaccine (live), plague vaccine, pneumococcal vaccine (polyvalent), poliovirus vaccine (inactivated), poliovirus vaccine (live, oral, trivalent), rabies vaccine (adsorbed), rabies vaccine (human
30 diploid cell), rubella and mumps virus vaccine (live), rubella virus vaccine (live, attenuated), tetanus toxoid (adsorbed), tetanus toxoid (fluid), typhoid vaccine (oral), typhoid vaccine (parenteral), typhoid Vi polysaccharide vaccine, varicella virus vaccine, yellow fever vaccine. The at least one antitoxin or antivenin can be at least one selected from black widow spider antivenin, Crotalidae antivenom (polyvalent), diphtheria antitoxin (equine), *Micruurus fulvius* antivenin). The at least one immune
35 serum can be at least one selected from cytomegalovirus immune globulin (intravenous), hepatitis B immune globulin (human), immune globulin intramuscular, immune globulin intravenous, rabies immune globulin (human), respiratory syncytial virus immune globulin intravenous (human), Rh₀(D)

- 5 immune globulin (human), Rh₀(D) immune globulin intravenous (human), tetanus immune globulin (human), varicella-zoster immune globulin. The at least one biological response modifiers can be at least one selected from aldesleukin, epoetin alfa, filgrastim, glatiramer acetate for injection, interferon alfacon-1, interferon alfa-2a (recombinant), interferon alfa-2b (recombinant), interferon beta-1a, interferon beta-1b (recombinant), interferon gamma-1b, levamisole hydrochloride, oprelvekin,
10 sargramostim. (See, e.g., pp. 964-1040 of *Nursing 2001 Drug Handbook*.)

The at least one ophthalmic anti-infectives can be selected from bacitracin, chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gentamicin sulfate, ofloxacin 0.3%, polymyxin B sulfate, sulfacetamide sodium 10%, sulfacetamide sodium 15%, sulfacetamide sodium 30%, tobramycin, vidarabine. The at least one ophthalmic anti-inflammatories can be at least one selected from
15 dexamethasone, dexamethasone sodium phosphate, diclofenac sodium 0.1%, fluorometholone, flurbiprofen sodium, ketorolac tromethamine, prednisolone acetate (suspension) prednisolone sodium phosphate (solution). The at least one miotic can be at least one selected from acetylcholine chloride, carbachol (intraocular), carbachol (topical), echothiopate iodide, pilocarpine, pilocarpine hydrochloride, pilocarpine nitrate. The at least one mydriatic can be at least one selected from atropine
20 sulfate, cyclopentolate hydrochloride, epinephrine hydrochloride, epinephryl borate, homatropine hydrobromide, phenylephrine hydrochloride, scopolamine hydrobromide, tropicamide. The at least one ophthalmic vasoconstrictors can be at least one selected from naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride. The at least one miscellaneous ophthalmics can be at least one selected from apraclonidine hydrochloride, betaxolol hydrochloride,
25 brimonidine tartrate, carteolol hydrochloride, dipivefrin hydrochloride, dorzolamide hydrochloride, emedastine difumarate, fluorescein sodium, ketotifen fumarate, latanoprost, levobunolol hydrochloride, metipranolol hydrochloride, sodium chloride (hypertonic), timolol maleate. The at least one otic can be at least one selected from boric acid, carbamide peroxide, chloramphenicol, triethanolamine polypeptide oleate-condensate. The at least one nasal drug can be at least one selected from
30 beclomethasone dipropionate, budesonide, ephedrine sulfate, epinephrine hydrochloride, flunisolide, fluticasone propionate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, triamcinolone acetonide, xylometazoline hydrochloride.
(See, e.g., pp. 1041-97 of *Nursing 2001 Drug Handbook*.)

The at least one local anti-infectives can be at least one selected from acyclovir, amphotericin B, azelaic acid cream, bacitracin, butoconazole nitrate, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamicin sulfate, ketoconazole, mafenide acetate, metronidazole (topical), miconazole nitrate, mupirocin, naftifine hydrochloride, neomycin sulfate, nitrofurazone, nystatin, silver

- 5 sulfadiazine, terbinafine hydrochloride, terconazole, tetracycline hydrochloride, tioconazole, tolnaftate. The at least one scabicide or pediculicide can be at least one selected from crotamiton, lindane, permethrin, pyrethrins. The at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone acetonide, 10 fluocinonide, flurandrenolide, fluticasone propionate, halcione, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, triamcinolone acetonide. (See, e.g., pp. 1098-1136 of *Nursing 2001 Drug Handbook*.)

The at least one vitamin or mineral can be at least one selected from vitamin A, vitamin B complex, cyanocobalamin, folic acid, hydroxocobalamin, leucovorin calcium, niacin, niacinamide, 15 pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, vitamin C, vitamin D, cholecalciferol, ergocalciferol, vitamin D analogue, doxercalciferol, paricalcitol, vitamin E, vitamin K analogue, phytonadione, sodium fluoride, sodium fluoride (topical), trace elements, chromium, copper, iodine, manganese, selenium, zinc. The at least one caloric can be at least one selected from amino acid infusions (crystalline), amino acid infusions in dextrose, amino acid infusions with electrolytes, amino acid infusions with electrolytes in dextrose, amino acid infusions for hepatic failure, amino acid infusions for high metabolic stress, amino acid infusions for renal failure, dextrose, fat emulsions, 20 medium-chain triglycerides. (See, e.g., pp. 1137-63 of *Nursing 2001 Drug Handbook*.)

CNGH0004 antibody or polypeptide compositions of the present invention can further comprise at least one of any suitable and/or effective amount of a composition or pharmaceutical 25 composition comprising at least one CNGH0004 protein or antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF 30 binding protein I or II (TBP-1 or TBP-II), nerelimonmab, infliximab, entercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., 35 aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a

5 thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an
10 antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limited to, any of IL-1 to IL-23. Suitable dosages are
15 well known in the art. See, e.g., Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, CT (2000); *PDR Pharmacopoeia*, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Such compositions can also include toxin molecules that are associated, bound, co-formulated
20 or co-administered with at least one antibody or polypeptide of the present invention. The toxin can optionally act to selectively kill the pathologic cell or tissue. The pathologic cell can be a cancer or other cell. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of ricin, diphtheria toxin, a venom toxin, or a bacterial toxin. The term toxin also includes both endotoxins and
25 exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal enterotoxin A (SEA), B (SEB), or C (SEC),
30 Streptococcal enterotoxins and the like. Such bacteria include, but are not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype 0157:H7), *Staphylococcus* species (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi*, *Salmonella cholera-suis*, *Salmonella enteritidis*), *Clostridium* species
35 (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni*, *Camphlobacter fetus*), *Helicobacter* species, (e.g., *Helicobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria*, *Aeromonas hydrophila*, *Aeromonas caviae*), *Plesiomonas*

- 5 *shigelloides*, *Yersina enterocolitica*, *Vibrios* species (e.g., *Vibrios cholerae*, *Vibrios parahemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp.239-254, Plenum Medical Book Co., New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference.

CNGH0004 antibody or polypeptide compounds, compositions or combinations of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the CNGH0004 antibody or polypeptide composition as well known in the art or as described herein.

Pharmaceutical excipients and additives useful in the present composition include but are not limited to polypeptides, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditol, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary but non-limiting polypeptide excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate

5 excipients for use in the present invention are mannitol, trehalose, and raffinose.

CNGH0004 antibody or polypeptide compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts such as citrate.

10 Additionally, CNGH0004 antibody or polypeptide compositions of the invention can include polymeric excipients/additives such as polyvinylpyrrolidones, flicols (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin), polyethylene glycols, flavoring agents, 15 antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for use in the CNGH0004 antibody or polypeptide compositions according to the invention are known in the art, e.g., 20 as listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents.

25 **Formulations**

As noted above, the invention provides for stable formulations, which is preferably a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one CNGH0004 antibody or polypeptide in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9,

5 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5,
4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-
2% m-cresol (e.g., 0.2, 0.3, 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0,
2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9,
1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01,
0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

10 As noted above, the invention provides an article of manufacture, comprising
packaging material and at least one vial comprising a solution of at least one CNGH0004 antibody or
polypeptide with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein
said packaging material comprises a label that indicates that such solution can be held over a period of
15 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further
comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized
at least one CNGH0004 antibody or polypeptide, and a second vial comprising an aqueous diluent of
prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a
patient to reconstitute the at least one CNGH0004 antibody or polypeptide in the aqueous diluent to
20 form a solution that can be held over a period of twenty-four hours or greater.

25 The at least one CNGH0004 antibody or polypeptide used in accordance with the present
invention can be produced by recombinant means, including from mammalian cell or transgenic
preparations, or can be purified from other biological sources, as described herein or as known in the
art.

30 The range of at least one CNGH0004 antibody in at least one product of the present invention
includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0
ng/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent
on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch,
pulmonary, transmucosal, or osmotic or micro pump methods.

35 The range of at least one CNGH0004 antibody in at least one product of the present invention
includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0
μg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent
on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch,
pulmonary, transmucosal, or osmotic or micro pump methods.

40 Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable
preservative. Preferred preservatives include those selected from the group consisting of phenol, m-
cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and

5 the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

Other excipients, e.g. isotonicity agents, buffers, antioxidants, preservative enhancers, can be
10 optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 15 6.0 to about 8.0. Preferably the formulations of the present invention have pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20
15 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyols, other block copolymers, and chelators such as EDTA and EGTA can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable 25 surfactant mitigates the propensity for the polypeptide to aggregate.

The formulations of the present invention can be prepared by a process which comprises mixing at least one CNGH0004 antibody or polypeptide and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one CNGH0004 antibody or polypeptide and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one CNGH0004 antibody or polypeptide in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the polypeptide 30 and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can 35

- 5 be optimized for the concentration and means of administration used.

The claimed formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial
10 requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

The present claimed articles of manufacture are useful for administration over a period of immediately to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be
15 safely stored at temperatures of from about 2 to about 40°C and retain the biologically activity of the polypeptide for extended periods of time, thus, allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

20 The solutions of at least one CNGH0004 antibody or polypeptide in the invention can be prepared by a process that comprises mixing at least one antibody or polypeptide in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody or polypeptide in water or buffer is combined in quantities sufficient to provide the polypeptide and optionally a preservative or
25 buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual vials
30 comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

The claimed products can be provided indirectly to patients by providing to
35 pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger

- 5 in size, providing a large reservoir from which smaller portions of the at least one antibody or polypeptide solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as BD Pens, BD Autojector®, Humaject®, NovoPen®, B-D®Pen, 10 AutoPen®, and OptiPen®, GenotropinPen®, Genotronorm Pen®, Humatrop Pen®, Reco-Pen®, Roferon Pen®, Biojector®, iject®, J-tip Needle-Free Injector®, Inraject®, Medi-Ject®, e.g., as made or developed by Becton Dickensen (Franklin Lakes, NJ, www.bectondickenson.com), Disetronic (Burgdorf, Switzerland, www.disetronic.com; Bioject, Portland, Oregon (www.bioject.com); National Medical Products , Weston Medical (Peterborough, UK, www.weston-medical.com), Medi-Ject Corp 15 (Minneapolis, MN, www.mediject.com). Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution such as the HumatropPen®.

The products presently claimed include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which 20 the product can be used. The packaging material of the present invention provides instructions to the patient to reconstitute the at least one CNGH0004 antibody or polypeptide in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the label indicates that such solution can be used over a period of 2-24 hours or greater. The presently claimed products are useful for human pharmaceutical 25 product use.

The formulations of the present invention can be prepared by a process that comprises mixing at least one CNGH0004 antibody or polypeptide and a selected buffer, preferably a phosphate buffer containing saline or a chosen salt. Mixing the at least one antibody or polypeptide and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a 30 suitable formulation, for example, a measured amount of at least one antibody or polypeptide in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the polypeptide and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all 35 factors that can be optimized for the concentration and means of administration used.

The claimed stable or preserved formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or

- 5 polypeptide that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

At least one CNGH0004 antibody or polypeptide in either the stable or preserved formulations 10 or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

Therapeutic Applications

15 The present invention also provides a method for modulating or treating at least one CNGH0004 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one antibody or polypeptide of the present invention.

The present invention also provides a method for modulating or treating at least one 20 CNGH0004 related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of obesity, an immune related disease, a cardiovascular disease, an infectious disease, a malignant disease or a neurologic disease.

The present invention also provides a method for modulating or treating at least one adult or pediatric immune or inflammation related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of, or at least one inflammation related to, rheumatoid arthritis, juvenile 25 rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, antiphospholipid syndrome, iridocyclitis, uveitis, optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis, Wegener's granulomatosis, sarcoidosis, orchitis, vasectomy or vasectomy reversal procedures, allergic atopic 30 diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma, hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, 35 rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, type I or type II diabetes, nephrosis, atopic diseases, hypersensitivity

- 5 reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, receptor hypersensitivity reactions, chronic obstructive pulmonary disease (COPD), Graves disease, Raynoud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, gene therapy inflammation (e.g., adenovirus, AAV, vaccinia, DNA or RNA, Muloney murine leukemia virus (MMLV) and the like),
- 10 type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo,
- 15 vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic, idiopathic, Wilson's disease, hemachromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, Hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease,
- 20 chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited to asthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like. See, e.g., the Merck Manual, 12th-17th Editions,
- 25 Merck & Company, Rahway, NJ (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook, Wells et al., eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), each entirely incorporated by reference.

The present invention also provides a method for modulating or treating at least one cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic atherosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system,

- 5 heart failure, cor pulmonale, primary pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris,
- 10 myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aortic and peripheral aneurysms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders, occlusive arterial disorders, peripheral atherosclerotic disease, thromboangiitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and
- 15 disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-reperfusion injury, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such
- 20 modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one infectious disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: acute or chronic infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection, HIV neuropathy, meningitis, hepatitis (A,B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome, thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory disease, orchitis, epididymitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemophagocytic syndrome, 25 vital encephalitis, aseptic meningitis, and the like. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of diphtheria toxin, a venom toxin, a viral toxin or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other

30 mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal

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- 5 enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins anthrax endotoxin, and the like. Such bacteria include, but are not limited to, gram negative or gram positive bacteria, *Bacillus*, *E. coli*, *Streptococcus*, *Staphylococcus*, *Shigella*, *Salmonella*, *Clostridium*, *Camphobacter*, *Heliobacter*, *Aeromonas*, *Enterococcus*, *Pseudomonas*, and the like, such as but not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype 0157:H7),
- 10 *Staphylococcus* species (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi*, *Salmonella cholera-suis*, *Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni*, *Camphlobacter fetus*), *Heliobacter* species, (e.g., *Heliobacter pylori*),
- 15 *Aeromonas* species (e.g., *Aeromonas sobria*, *Aeromonas hydrophila*, *Aeromonas caviae*), *Plesiomonas shigelloides*, *Yersina enterocolitica*, *Vibrios* species (e.g., *Vibrios cholerae*, *Vibrios parahaemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co.,
- 20 New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.
- 25

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chromic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, Hodgkin's lymphoma, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma,

- 5 testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like.

Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

- 10 The present invention also provides a method for modulating or treating at least one neurologic disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerorden-Spatz disease; and Dementia pugilistica, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. See, e.g., the Merck Manual, 16th Edition, Merck & Company, Rahway, NJ (1992).

- Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.
- 35 Such a method can optionally further comprise co-administration or combination therapy for treating such diseases, wherein the administering of said at least one CNGH0004 antibody or polypeptide, specified portion or variant thereof, further comprises administering, before concurrently, and/or after,

- 5 at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-1 or TBP-II), nerelimonmab, infliximab, enteracept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin,
- 10 aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an
- 15 antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone
- 20 replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable
- 25 dosages are well known in the art. See, e.g., Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR *Pharmacopoeia*, Tarascon Pocket *Pharmacopoeia* 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

TNF antagonists suitable for compositions, combination therapy, co-administration, devices and/or methods of the present invention (further comprising at least one anti body, specified portion and variant thereof, of the present invention), include, but are not limited to, TNF antibodies, antigen-binding fragments thereof, and receptor molecules which bind specifically to TNF; compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g., pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers; compounds which prevent and/or inhibit TNF receptor signalling, such as mitogen activated polypeptide (MAP) kinase inhibitors; compounds which block and/or inhibit membrane TNF cleavage, such as metallopolypeptidase inhibitors; compounds which

- 5 block and/or inhibit TNF activity, such as angiotensin converting enzyme (ACE) inhibitors (e.g., captopril); and compounds which block and/or inhibit TNF production and/or synthesis, such as MAP kinase inhibitors.

As used herein, a "tumor necrosis factor antibody," "TNF antibody," "TNF α antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNF α activity *in vitro*, *in situ* and/or preferably *in vivo*. For example, a suitable TNF human antibody of the present invention can bind TNF α and includes TNF antibodies, antigen-binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNF α . A suitable TNF antibody or fragment can also decrease block, abrogate, interfere, prevent and/or inhibit TNF RNA, DNA or polypeptide synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.

Chimeric antibody cA2 consists of the antigen binding variable region of the high-affinity neutralizing mouse human TNF α IgG1 antibody, designated A2, and the constant regions of a human IgG1, kappa immunoglobulin. The human IgG1 Fc region improves allogeneic antibody effector function, increases the circulating serum half-life and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric antibody cA2 is derived from the variable region of the murine antibody A2. In a particular embodiment, a preferred source for nucleic acids encoding the variable region of the murine antibody A2 is the A2 hybridoma cell line.

Chimeric A2 (cA2) neutralizes the cytotoxic effect of both natural and recombinant human TNF α in a dose dependent manner. From binding assays of chimeric antibody cA2 and recombinant human TNF α , the affinity constant of chimeric antibody cA2 was calculated to be $1.04 \times 10^{10} M^{-1}$. Preferred methods for determining monoclonal antibody specificity and affinity by competitive inhibition can be found in Harlow, *et al.*, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988; Colligan *et al.*, eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, New York, (1992-2000); Kozbor *et al.*, *Immunol. Today*, 4:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, New York (1987-2000); and Muller, *Meth. Enzymol.*, 92:589-601 (1983), which references are entirely incorporated herein by reference.

In a particular embodiment, murine monoclonal antibody A2 is produced by a cell line designated c134A. Chimeric antibody cA2 is produced by a cell line designated c168A.

Additional examples of monoclonal TNF antibodies that can be used in the present invention are described in the art (see, e.g., U.S. Patent No. 5,231,024; Möller, A. *et al.*, *Cytokine* 2(3):162-169 (1990); U.S. Application No. 07/943,852 (filed September 11, 1992); Rathjen *et al.*, International

- 5 Publication No. WO 91/02078 (published February 21, 1991); Rubin *et al.*, EPO Patent Publication
No. 0 218 868 (published April 22, 1987); Yone *et al.*, EPO Patent Publication No. 0 288 088 (October
26, 1988); Liang, *et al.*, *Biochem. Biophys. Res. Comm.* 137:847-854 (1986); Meager, *et al.*,
Hybridoma 6:305-311 (1987); Fendly *et al.*, *Hybridoma* 6:359-369 (1987); Bringman, *et al.*,
Hybridoma 6:489-507 (1987); and Hirai, *et al.*, *J. Immunol. Meth.* 96:57-62 (1987), which references
10 are entirely incorporated herein by reference).

TNF Receptor Molecules

Preferred TNF receptor molecules useful in the present invention are those that bind TNF α with high affinity (see, e.g., Feldmann *et al.*, International Publication No. WO 92/07076 (published April 30, 1992); Schall *et al.*, *Cell* 61:361-370 (1990); and Loetscher *et al.*, *Cell* 61:351-359 (1990), which references are entirely incorporated herein by reference) and optionally possess low immunogenicity. In particular, the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNF cell surface receptors are useful in the present invention. Truncated forms of these receptors, comprising the extracellular domains (ECD) of the receptors or functional portions thereof (see, e.g., Corcoran *et al.*, *Eur. J. Biochem.* 223:831-840 (1994)), are also useful in the present invention. Truncated forms of the TNF receptors, comprising the ECD, have been detected in urine and serum as 30 kDa and 40 kDa TNF α inhibitory binding polypeptides (Engelmann, H. *et al.*, *J. Biol. Chem.* 265:1531-1536 (1990)). TNF receptor multimeric molecules and TNF immunoreceptor fusion molecules, and derivatives and fragments or portions thereof, are additional examples of TNF receptor molecules which are useful in the methods and compositions of the present invention. The TNF receptor molecules which can be used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, can contribute to the therapeutic results achieved.

TNF receptor multimeric molecules useful in the present invention comprise all or a functional portion of the ECD of two or more TNF receptors linked via one or more polypeptide linkers or other nonpeptide linkers, such as polyethylene glycol (PEG). The multimeric molecules can further comprise a signal peptide of a secreted polypeptide to direct expression of the multimeric molecule. These multimeric molecules and methods for their production have been described in U.S. Application No. 08/437,533 (filed May 9, 1995), the content of which is entirely incorporated herein by reference.

TNF immunoreceptor fusion molecules useful in the methods and compositions of the present invention comprise at least one portion of one or more immunoglobulin molecules and all or a functional portion of one or more TNF receptors. These immunoreceptor fusion molecules can be assembled as monomers, or hetero- or homo-multimers. The immunoreceptor fusion molecules can

- 5 also be monovalent or multivalent. An example of such a TNF immunoreceptor fusion molecule is TNF receptor/IgG fusion polypeptide. TNF immunoreceptor fusion molecules and methods for their production have been described in the art (Lesslauer *et al.*, *Eur. J. Immunol.* 21:2883-2886 (1991); Ashkenazi *et al.*, *Proc. Natl. Acad. Sci. USA* 88:10535-10539 (1991); Peppel *et al.*, *J. Exp. Med.* 174:1483-1489 (1991); Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219 (1994); Butler *et al.*, *Cytokine* 6(6):616-623 (1994); Baker *et al.*, *Eur. J. Immunol.* 24:2040-2048 (1994); Beutler *et al.*, U.S. Patent No. 5,447,851; and U.S. Application No. 08/442,133 (filed May 16, 1995), each of which references are entirely incorporated herein by reference). Methods for producing immunoreceptor fusion molecules can also be found in Capon *et al.*, U.S. Patent No. 5,116,964; Capon *et al.*, U.S. Patent No. 5,225,538; and Capon *et al.*, *Nature* 337:525-531 (1989), which references are entirely 10 incorporated herein by reference.
- 15

A functional equivalent, derivative, fragment or region of TNF receptor molecule refers to the portion of the TNF receptor molecule, or the portion of the TNF receptor molecule sequence which encodes TNF receptor molecule, that is of sufficient size and sequences to functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF? with high affinity and possess low immunogenicity). A functional equivalent of TNF receptor molecule also includes modified TNF receptor molecules that functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF? with high affinity and possess low immunogenicity). For example, a functional equivalent of TNF receptor molecule can contain a "SILENT" codon or one or more amino acid substitutions, deletions or additions (e.g., substitution of one acidic amino acid for another acidic amino acid; or substitution of one codon encoding the same or different hydrophobic amino acid for another codon encoding a hydrophobic amino acid). See Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Assoc. and Wiley-Interscience, New York (1987-2000).

30 Cytokines include any known cytokine. See, e.g., CopewithCytokines.com. Cytokine antagonists include, but are not limited to, any antibody, fragment or mimetic, any soluble receptor, fragment or mimetic, any small molecule antagonist, or any combination thereof.

Therapeutic Treatments. Any method of the present invention can comprise a method for treating a CNGH0004 mediated disorder or disease, comprising administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or 35 polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such disorders or diseases, wherein the administering of said at least one CNGH0004 antibody or

- 5 polypeptide, further comprises administering, before concurrently, and/or after, at least one selected from at least one at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist.
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Polypeptide Dosing

- 25 Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 polypeptide composition that total, on average, a range from at least about 0.001 ng to 500 milligrams of at least one CNGH0004 polypeptide per kilogram of patient per dose, and preferably from at least about 0.1 ng to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition.
- 30 Alternatively, the effective serum concentration can comprise 0.0001ng –0.05 mg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual
- 35 administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

5 Preferred doses of at least one polypeptide can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 micrograms or
10 milligrams/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 15 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 ng or μ g/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the
20 pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 μ g to 100 milligrams per kilogram of body weight. Ordinarily 0.0001 to 50, and preferably 0.001 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.
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As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 μ g/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000 or 3000 μ g/kg,
30 per day, or 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 35 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

- 5 Dosage forms (composition) suitable for internal administration generally contain from about 0.00001 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.
- 10 Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 antibody composition that total, on average, a range from at least about 0.00001 to 500 milligrams of at least one CNGH0004 antibody per kilogram of patient per dose, and preferably from at least about 0.0001 to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition.
- 15 Alternatively, the effective serum concentration can comprise 0.0001-500 µg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired 20 daily dose or effect is achieved.

Antibody Dosing

- Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 antibody composition that total, on average, a range from at least about 0.001 ng to 500 milligrams of at least one CNGH0004 antibody per kilogram of patient per dose, and 25 preferably from at least about 0.1 ng to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition.
- Alternatively, the effective serum concentration can comprise 0.0001ng –0.05 mg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, 30 and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

- Preferred doses of at least one antibody can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 35 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87,

- 5 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 mg/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5,
- 10 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 µg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and preferably 0.1 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.1 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

35 Administration

For parenteral administration, the antibody or polypeptide can be formulated as a solution, suspension, emulsion or lyophilized powder in association, or separately provided, with a

5 pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 1-10% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

10 Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Alternative Administration

15 Many known and developed modes of can be used according to the present invention for administering pharmaceutically effective amounts of at least one CNGH0004 antibody according to the present invention. While pulmonary administration is used in the following description, other modes of administration can be used according to the present invention with suitable results.

CNGH0004 antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

20 **Parenteral Formulations and Administration**

Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for 25 injection can be a non-toxic, non-orally administrable diluting agent such as aqueous solution or a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent, or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or 30 semisynthetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 entirely incorporated herein by reference.

Alternative Delivery

35 The invention further relates to the administration of at least one CNGH0004 antibody by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic,

5 intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. At least one CNGH0004 antibody composition can be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) or any other administration particularly in the form of liquid solutions or suspensions; for use in vaginal or
10 rectal administration particularly in semisolid forms such as, but not limited to, creams and suppositories; for buccal, or sublingual administration such as, but not limited to, in the form of tablets or capsules; or intranasally such as, but not limited to, the form of powders, nasal drops or aerosols or certain agents; or transdermally such as not limited to a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure
15 or to increase the drug concentration in the transdermal patch (Junginger, et al. In "Drug Permeation Enhancement"; Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, entirely incorporated herein by reference), or with oxidizing agents that enable the application of formulations containing polypeptides and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways such as electroporation, or to increase the mobility of charged drugs
20 through the skin such as iontophoresis, or application of ultrasound such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being entirely incorporated herein by reference).

Pulmonary/Nasal Administration

For pulmonary administration, preferably at least one CNGH0004 antibody composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. According to the invention, at least one CNGH0004 antibody can be delivered by any of a variety of inhalation or nasal devices known in the art for administration of a therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal administration of antibodies are also known in the art. All such devices can use of formulations suitable for the administration for the dispensing of antibody in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non aqueous) or solid particles. Metered dose inhalers like the Ventolin® metered dose inhaler, typically use a propellant gas and require actuation during inspiration (See, e.g., WO 94/16970, WO 98/35888). Dry powder inhalers like Turbuhaler™ (Astra), Rotahaler® (Glaxo), Diskus® (Glaxo), Spiros™ inhaler (Dura), devices marketed by Inhale Therapeutics, and the Spinhaler® powder inhaler (Fisons), use breath-actuation of a mixed powder (US 4668218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO
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35

- 5 94/08552 Dura, US 5458135 Inhale, WO 94/06498 Fisons, entirely incorporated herein by reference).
Nebulizers like AERx™ Aradigm, the Ultravent® nebulizer (Mallinckrodt), and the Acorn II® nebulizer
(Marquest Medical Products) (US 5404871 Aradigm, WO 97/22376), the above references entirely
incorporated herein by reference, produce aerosols from solutions, while metered dose inhalers, dry
powder inhalers, etc. generate small particle aerosols. These specific examples of commercially
10 available inhalation devices are intended to be a representative of specific devices suitable for the
practice of this invention, and are not intended as limiting the scope of the invention. Preferably, a
composition comprising at least one CNGH0004 antibody is delivered by a dry powder inhaler or a
sprayer. There are several desirable features of an inhalation device for administering at least one
15 antibody of the present invention. For example, delivery by the inhalation device is advantageously
reliable, reproducible, and accurate. The inhalation device can optionally deliver small dry particles,
e.g. less than about 10 µm, preferably about 1-5 µm, for good respirability.

Administration of CNGH0004 antibody Compositions as a Spray

A spray including CNGH0004 antibody composition can be produced by forcing a suspension
or solution of at least one CNGH0004 antibody through a nozzle under pressure. The nozzle size and
20 configuration, the applied pressure, and the liquid feed rate can be chosen to achieve the desired output
and particle size. An electrospray can be produced, for example, by an electric field in connection with
a capillary or nozzle feed. Advantageously, particles of at least one CNGH0004 antibody composition
delivered by a sprayer have a particle size less than about 10 µm, preferably in the range of about 1 µm
to about 5 µm, and most preferably about 2 µm to about 3 µm.

25 Formulations of at least one CNGH0004 polypeptide or antibody composition suitable for use
with a sprayer typically include antibody or polypeptide compositions in an aqueous solution at a
concentration of about 0.0000001 mg to about 1000 mg of at least one CNGH0004 antibody or
polypeptide composition per ml of solution or mg/gm, or any range or value therein, e.g., but not limited
to, .1, .2, .3, .4, .5, .6, .7, .8, .9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22,
30 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 ng or µg or mg/ml or ng or µg or mg/gm.
The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative,
a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for
stabilization of the antibody composition, such as a buffer, a reducing agent, a bulk polypeptide, or a
carbohydrate. Bulk polypeptides useful in formulating antibody compositions include albumin,
35 protamine, or the like. Typical carbohydrates useful in formulating antibody compositions include
sucrose, mannitol, lactose, trehalose, glucose, or the like. The antibody composition formulation can
also include a surfactant, which can reduce or prevent surface-induced aggregation of the antibody or

- 5 polypeptide composition caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between 0.001 and 14% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like. Additional agents
10 known in the art for formulation of a polypeptide such as CNGH0004 antibodies, or specified portions or variants, can also be included in the formulation.

Administration of CNGH0004 antibody compositions by a Nebulizer

Antibody composition can be administered by a nebulizer, such as jet nebulizer or an ultrasonic nebulizer. Typically, in a jet nebulizer, a compressed air source is used to create a high-velocity air jet through an orifice. As the gas expands beyond the nozzle, a low-pressure region is created, which draws a solution of antibody composition through a capillary tube connected to a liquid reservoir. The liquid stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types can be employed to achieve the desired performance characteristics from a given jet nebulizer. In an ultrasonic nebulizer, high-frequency electrical energy is used to create vibrational, mechanical energy, typically employing a piezoelectric transducer. This energy is transmitted to the formulation of antibody composition either directly or through a coupling fluid, creating an aerosol including the antibody composition. Advantageously, particles of antibody composition delivered by a nebulizer have a particle size less than about 10 μm , preferably in the range of about 1 μm to about 5 μm , and most preferably about 2 μm to about 3 μm .

Formulations of at least one CNGH0004 antibody suitable for use with a nebulizer, either jet or ultrasonic, typically include a concentration of about 0.1 mg to about 100 mg of at least one CNGH0004 antibody polypeptide per ml of solution. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The 30 formulation can also include an excipient or agent for stabilization of the at least one CNGH0004 antibody composition, such as a buffer, a reducing agent, a bulk polypeptide, or a carbohydrate. Bulk polypeptides useful in formulating at least one CNGH0004 antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one CNGH0004 antibody include sucrose, mannitol, lactose, trehalose, glucose, or the like. The at least one CNGH0004 antibody formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the at least one CNGH0004 antibody caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid

5 esters and alcohols, and polyoxyethylene sorbital fatty acid esters. Amounts will generally range between 0.001 and 4% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan mono-oleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a polypeptide such as antibody polypeptide can also be included in the formulation.

10 **Administration of CNGH0004 antibody compositions By A Metered Dose Inhaler**

In a metered dose inhaler (MDI), a propellant, at least one CNGH0004 antibody, and any excipients or other additives are contained in a canister as a mixture including a liquefied compressed gas. Actuation of the metering valve releases the mixture as an aerosol, preferably containing particles in the size range of less than about 10 μm , preferably about 1 μm to about 5 μm , and most preferably about 2 μm to about 3 μm . The desired aerosol particle size can be obtained by employing a formulation of antibody composition produced by various methods known to those of skill in the art, including jet-milling, spray drying, critical point condensation, or the like. Preferred metered dose inhalers include those manufactured by 3M or Glaxo and employing a hydrofluorocarbon propellant.

Formulations of at least one CNGH0004 antibody for use with a metered-dose inhaler device will generally include a finely divided powder containing at least one CNGH0004 antibody as a suspension in a non-aqueous medium, for example, suspended in a propellant with the aid of a surfactant. The propellant can be any conventional material employed for this purpose, such as chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, HFA-134a (hydrofluoroalkane-134a), HFA-227 (hydrofluoroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one CNGH0004 antibody as a suspension in the propellant, to protect the active agent against chemical degradation, and the like. Suitable surfactants include sorbitan trioleate, soya lecithin, oleic acid, or the like. In some cases solution aerosols are preferred using solvents such as ethanol. Additional agents known in the art for formulation of a polypeptide such as polypeptide can also be included in the formulation.

One of ordinary skill in the art will recognize that the methods of the current invention can be achieved by pulmonary administration of at least one CNGH0004 antibody compositions via devices not described herein.

35 **Oral Formulations and Administration**

Formulations for oral rely on the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase

- 5 artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylo) to inhibit enzymatic degradation. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum
- 10 tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, alpha.-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.
- 15 Tablets and pills can be further processed into enteric-coated preparations. The liquid preparations for oral administration include emulsion, syrup, elixir, suspension and solution preparations allowable for medical use. These preparations can contain inactive diluting agents ordinarily used in said field, e.g., water. Liposomes have also been described as drug delivery systems for insulin and heparin (U.S. Pat. No. 4,239,754). More recently, microspheres of artificial polymers
- 20 of mixed amino acids (polypeptideoids) have been used to deliver pharmaceuticals (U.S. Pat. No. 4,925,673). Furthermore, carrier compounds described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,5,871,753 are used to deliver biologically active agents orally are known in the art.

Mucosal Formulations and Administration

For absorption through mucosal surfaces, compositions and methods of administering at least one CNGH0004 antibody include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. Nos. 5,514,670). Mucous surfaces suitable for application of the emulsions of the present invention can include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, e.g. suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration excipients include sugars, calcium stearate, magnesium stearate, pregelatinated starch, and the like (U.S. Pat. Nos. 35 5,849,695).

Transdermal Formulations and Administration

For transdermal administration, the at least one CNGH0004 antibody is encapsulated in a

- 5 delivery device such as a liposome or polymeric nanoparticles, microparticle, microcapsule, or
microspheres (referred to collectively as microparticles unless otherwise stated). A number of suitable
devices are known, including microparticles made of synthetic polymers such as polyhydroxy acids
such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and
polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other
10 polypeptides, alginate and other polysaccharides, and combinations thereof (U.S. Pat. Nos. 5,814,599).

Prolonged Administration and Formulations

It can be sometimes desirable to deliver the compounds of the present invention to the subject
over prolonged periods of time, for example, for periods of one week to one year from a single
administration. Various slow release, depot or implant dosage forms can be utilized. For example, a
15 dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low
degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as
phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid,
polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a
salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum,
20 copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-
dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) e.g. a zinc tannate
salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt
such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel
with, e.g. sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts,
25 pamoate salts, and the like. Another type of slow release depot formulation for injection would contain
the compound or salt dispersed for encapsulated in a slow degrading, non-toxic, non-antigenic polymer
such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No.
3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above can
also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow
30 release, depot or implant formulations, e.g. gas or liquid liposomes are known in the literature (U.S.
Pat. Nos. 5,770,222 and "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson
ed., Marcel Dekker, Inc., N.Y., 1978).

Having generally described the invention, the same will be more readily understood by
35 reference to the following examples, which are provided by way of illustration and are not intended as
limiting.

5 Example 1: Cloning and Expression of CNGH0004 polypeptide or antibody in Mammalian Cells

A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of mRNA, the polypeptide or antibody coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., RSV, HTLV, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pIREs1neo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clonetech Labs, Palo Alto, CA), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Mammalian host cells that could be used include human Hela 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the gene can be expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded polypeptide or antibody, e.g., as a desired portion of at least one of SEQ ID NO:1. The DHFR (dihydrofolate reductase) marker is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277-279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are used for the production of antibodies or polypeptides of the present invention.

The expression vectors pC1 and pC4 contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment of the CMV-enhancer (Boshart, et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

5 **Cloning and Expression in CHO Cells**

The vector pC4 is used for the expression of CNGH0004 antibody or polypeptide, e.g., using a coding sequence for at least one of SEQ ID NO:1, such as but not limited to SEQ ID NO:2. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (e.g., alpha minus MEM, Life Technologies, Gaithersburg, MD) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., F. W. Alt, et al., J. Biol. Chem. 253:1357-1370 (1978); J. L. Hamlin and C. Ma, Biochem. et Biophys. Acta 1097:107-143 (1990); and M. J. Page and M. A. Sydenham, Biotechnology 9:64-68 (1991)). Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained that contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains coding DNA for expressing the gene of interest under control of the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV) (Boshart, et al., Cell 41:521-530 (1985)). Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human b-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLV. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the CNGH0004 polypeptide in a regulated way in mammalian cells (M. Gossen, and H. Bujard, Proc. Natl. Acad. Sci. USA 89: 5547-5551 (1992)). For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It can be advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf

- 5 intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

The DNA sequence encoding the desired CNGH0004 antibody or polypeptide is used, e.g., DNA or RNA coding for at least one of SEQ ID NO:1, such as but not limited to SEQ ID NO:2 corresponding to at least one portion of at least one CNGH0004 antibody polypeptide of the present invention, according to known method steps.

The isolated encoding DNA and the dephosphorylated vector are then ligated with T4 DNA ligase. E. coli HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. 5
15 μ g of the expression plasmid pC4 is cotransfected with 0.5 μ g of the plasmid pSV2-neo using lipofectin. The plasmid pSV2neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 μ g /ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with
20 10, 25, or 50 ng/ml of methotrexate plus 1 μ g /ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is
25 repeated until clones are obtained that grow at a concentration of 100 - 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reverse phase HPLC analysis.

Example 2: Discovery of CNGH0004 nucleic acid and amino acid sequences and fragments and domains thereof

Skin biopsy samples were collected from patients with moderate to severe psoriasis. Seven samples were obtained at baseline (week 0) from lesional sites. Five were obtained from lesional site at 2 weeks post-infliximab treatment. Total RNA were extracted from each biopsy sample and were hybridized to two different types of cDNA arrays. RNA preparation, labeling, and hybridization were 35 performed as reported previously (9). Raw intensity data from the cDNA arrays were first normalized within each sample. Linear normalization and then nonlinear normalization was performed within each sample. Outlier intensity data points (greater than 1.4 fold away from the median of replicate

5 measurements) were identified and removed from the data sets. The average intensity was generated by calculating the arithmetic mean of nonoutlier intensity values. Spline normalization of the average intensity was then performed across all samples in the data sets. Sample comparison was made between week 0 and week 2.

10 Data mining was performed using OmniViz software (Maynard, MA). Data comparisons were expressed as ratios in OmniViz and the \log_2 of ratios were used to cluster expression data. Clustering was performed first using the Kmeans method. All genes were filtered by a single fold change greater than or equal to 2 for either increase or decrease in expression. Genes that past the filters were then clustered using a hierarchical method and correlation metric.

Description of CNGH0004 gene

15 CNGH0004 is located on Chromosome 9q31.3, from nucleotide 1065860007 to 106800277 on the minus strand based on the human reference sequence (UCSC version hg15, which is based on NCBI Build 33 and was produced by the International Human Genome Sequencing Consortium). The human genome sequence covers about 99 percent of the gene-containing regions in the genome, and has been sequenced to an accuracy of 99.99 percent. CNGH0004 neighbors MUSK gene at 5' end and
20 TXN gene at 3' end. The gene is 214270 base pairs long, spreading over three BACs, AL592463, AL354982, and AL158158 from 5' to 3'.

25 Known mRNAs mapped to this region include Homo sapiens likely ortholog of mouse polydom (NM_024500), Homo sapiens cDNA FLJ14964 fis(AK027870), Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 248114 (AL079279), Homo sapiens serologically defined breast cancer antigen NY-BR-38 mRNA (AF308289), and Homo sapiens cDNA FLJ13529 fis (AK023591).

CNGH0004 transcript is 11,996 bp long. The transcript includes 5' UTR of 1000 bp, 48 exons, and 3' UTR of 280 bp. The ployA signal sequence is not identified.

30 Polymorphism analysis against public SNP database (<http://www.ncbi.nlm.nih.gov/SNP/>) as well as NM_024500 revealed 12 SNPs within CNGH0004 coding region (CDS). Eight of the 12 changes result in non-synonymous changes at amino acid level (Table 1).

Conceptual translation of CNGH0004 results in a polypeptide of 3571 amino acid residues. It shares 81.7% residues with mouse Polydom (10) across the entire length and seems to be an ortholog of the mouse protein.

35 Both proteins share significant overall domain structures: an N-terminal signal peptide followed by a Von Willebrand factor (VWA) domain, 3 CCP (Sushi) domains, 2 Hyalin domains, 1 more CCP domain, 6 EGF-like domains, a Pentaxin domain, 2 more CCP domains, one EGF-like

5 domain, 28 more CCP domains, and 3 more EGF-like domains at the very C-terminus. There is another unclassified cystein-rich domain (pfam-B 232) that repeated 4 times at the N-terminal portion of the protein (Table 2).

Sequence analysis shows that CNGH0004 and mouse Polydom represent a new sub-family within the EGF superfamily of protein. The members of this sub-family include Q9VM55 of 10 *Drosophila melanogaster*; and Q20535 of *C. elegans*. The common signature of this family is a combination of CCP, EGF-like and Hyalin domain, often repeated many times. Based on the distribution pattern of these domains in other proteins, CNGH0004 protein can be classified as a secreted extracellular matrix protein probably involves in tissue remodeling.

VWA domains in extracellular eukaryotic proteins mediate adhesion via metal ion-dependent 15 adhesion sites (MIDAS). It has been implicated in the immune and haemostatic systems, cell adhesion or matrix assembly (11).

CCP domain, also known as Sushi repeat or short complement-like repeat (SCR), is approximately 60 amino acid residues long and has been identified in most components and regulatory 20 proteins of the complement cascade. Prototype members of this protein family are molecules that regulate the complement system (12, 13). CCP repeats have also been identified in the selectin family of adhesion molecules. CCP modules contain proteins of the complement system (14).

Hyalin Repeat, also known as HYR domain, is named after the protein hyalin that is composed exclusively of this repeat. This domain probably corresponds to a new superfamily in the immunoglobulin fold. This domain may be involved in cell adhesion (15).

25 EGF-like (including EGF_CA) domain is found in the sequence of epidermal growth factor (EGF) and in a large number of membrane-bound and extracellular proteins with various biological functions such as blood coagulation, control of cell fate, cell adhesion, activation of complement and fibrinolysis (16, 17). Many of these proteins require calcium for their biological function. A calcium-binding site has been found to be located at the N-terminus of the EGF-like domains. Calcium-binding 30 may be crucial for numerous protein-protein interactions.

Pentaxins (or pentraxins) are a family of proteins that show, under electron microscope, a discoid arrangement of five noncovalently bound subunits. Proteins of the pentraxin family are involved in acute immunological responses. PTX domain mediates binding of a variety of ligands which is Calcium-dependent (18).

35

Example 3: Expression of CNGH0004 in normal and diseased human tissues

We queried microarray expression database at Johnson & Johnson Pharmaceutical R&D at La

5 Jolla, as well as public expression database such as SAGE (<http://www.ncbi.nlm.nih.gov/SAGE/>). CNGH0004 gene is expressed at a high level in normal placenta and fetal tissues. It's at a lower, but detectable level in adult tissues including breast, ear, heart, pancreas, nose, and brain tissues.

We validated the above findings with real-time quantitative PCR using ABI Prism 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). Human tissue master plate was
10 prepared according to Pinhasov et al (19). Total RNA from 83 representative human tissues was purchased from Strategene (La Jolla, CA).

Two primer-probe sets were ordered from Applied Biosystem as their Assays-on-Demand™ Gene Expression Products (Foster City, CA): Hs00225829_m1, which covers sequence GGTGTGTGGAGCGCCACTGTTCCAC that correspond to 2475 –2499 of CNGH0004; and
15 Hs00295944_m1, which covers sequence ATGCAAAGAGACCAGGTGTGAAACT that coresnd to 10879 –10903 of CNGH0004. As shown in Table 3, both primer-probes sets yield similar results that are in agreement with *in silico* findings.

Expression of CNGH0004 in most human tissues is very low (table 3). Moderate expression can be detected in adrenal, colon, lung, ovary, pericardium, skin, spleen, stomach, testis, and thymus.
20 The highest expression by far is in placenta, which is at least over 20-fold increase compared to those tissues with moderate expression. CNGH0004 is virtually undetectable in the 10 cell lines we tested.

In certain cancer tissues, however, CNGH0004 expression is significantly elevated. These include glioblastoma, melanoma, colon epithelia, prostate carcinoma, ovary serous adenocarcinoma, pancreas neoplasia, and stomach adeno-carcinoma.

25 CNGH0004 is also detected at above normal levels in asthmatic airway smooth muscle cells.

Expression level of CNGH0004 is lower in psoriatic lesional areas as compared to non-lesional areas. REMICADE treatment restores its level back to normal.

Example 4: CNGH0004 involvement in cell migration and invasion of metastasis tumors

30 The establishment of metastasis requires that tumor cells acquire new adhesion and migration properties to emigrate from primary sites and colonize distant organs. CNGH0004 is a cell membrane protein often overexpressed on tumor cells and, being both a cell-cell and cell-extracellular matrix adhesion protein, is well positioned to contribute to this process. Indeed, a fragment of CNGH0004 was identified as serologically defined breast cancer antigen NY-BR-38 mRNA. Furthermore, the
35 interaction of CNGH0004 with other cellular proteins involved in motogenesis and proteolysis is a determinant factor in cell migration and invasion.

The role of CNGH0004 in angiogenesis can also be investigated using *in vitro* cell migration

5 and invasion assays. Human microvascular endothelial cells (HMVEC) transfected with CNGH0004 gene, or its antisense, or siRNA constructs, are seeded in the top wells of the transwell system, in cell medium containing 1% FBS. In the bottom wells, culturing medium with 10% FBS serve as a chemotactic source to induce cell migration or invasion. The top and bottom wells are separated by a membrane with pores of 8 µm in diameter. The membrane is either uncoated or coated with various
10 extracellular matrix proteins, i.e., collagen, fibronectin, vitronectin, or Matrigel, for determining cell migration or invasion. It is expected that modulation of CNGH0004 changes the properties of endothelial cell migration and invasion stimulation. The specificity of CNGH0004 in endothelial cell migration and invasion are investigated using CNGH0004 antibody of the present invention. Such antibodies block at least one biological activity of CNGH0004.

15

Advantage/Utilities

CNGH0004 gene is a human ortholog of the mouse Polydom gene. After conceptual translation, the two proteins share extensive homology (81.7%) that is also reflected on their protein domain patterns. The extremely high evolutional conservation implied that the function of CNGH0004
20 and Polydom is essential to human and mouse, respectively. It is also evident from its ubiquitous expression pattern in embryonic tissues in human and mouse.

Based on N-terminal signal peptide, CNGH0004 protein is predicted to be an extracellular matrix protein. All CNGH0004 protein domains are characterized as extracellular domains.

With 10 EGF domains, which tend to be glycosylated, CNGH0004 is likely to be post-
25 translationally modified (PTM), such as glycosylation. With its high molecular weight and the possible PTM, CNGH0004 is likely distributed in the vicinity of cells that express it. As a target, it is amendable for localized treatment such as subcutaneous injection. Since it is accessible for antagonists and agonists thereto including monoclonal antibodies, vaccines, and adjuvants. CNGH0004 can well be suited for an antibody target.

30 In addition to normal placenta and fetal tissue development, protein domains that constitute CNGH0004 are probably also involved in tissue remodeling of airway smooth muscle as well as psoriatic epithelium. Based on its domain structure, CNGH0004 may function through mediating adhesion via metal ion-dependent adhesion sites (MIDAS), or via modulating complement control related to immunological responses. As such, CNGH0004 is a potential therapeutic target for treatment
35 of autoimmune or chronic inflammatory diseases including, but not limited to psoriasis or asthma, and different types of cancers.

5 Table 1. Non-synonymous SNPs within CNGH0004

Nucleotide position	Nucleotide change	Amino acid position	Amino acid change
2286	C->T	429	Ser->Leu
2519	G->A	507	Val->Ile
3526	C->G	842	Cys ->Trp
3939	A->G	980	Glu ->Gly
4188	A->G	1063	Tyr->Cyc
5246	A->C	1416	Lys->Gln
5325	A->T	1442	Asp->Val
6429	C->A	A1810E	Ala->Glu

Table 2. Protein domains and locations on CNGH0004.

10

Domain Name	Pfam ID	Start residue	End residue
Signal Peptide		1	41
VWA		83	259
Pfam-B_232		305	360
Sushi/CCP	PF00084	378	433
Sushi/CCP	PF00084	438	493
Sushi/CCP	PF00084	498	559
HYR	PF02494	561	642
HYR	PF02494	643	722
CCP	PF00084	727	787
Pfam-B_232		999	1036
Pfam-B_232		1041	1106
Pfam-B_232		1108	1160
EGF-like	PF00008	1196	1229
EGF-like	PF00008	1231	1267
EGF-like	PF00008	1269	1305
EGF-like	PF00008	1307	1343
EGF-like	PF00008	1345	1381

EGF-like	PF00008	1383	1419
Pentaxin		1431	1623
Sushi/CCP	PF00084	1631	1685
Sushi/CCP	PF00084	1690	1743
EGF-like	PF00008	1748	1784
Sushi/CCP	PF00084	1789	1842
Sushi/CCP	PF00084	1847	1900
Sushi/CCP	PF00084	1905	1958
Sushi/CCP	PF00084	1963	2016
Sushi/CCP	PF00084	2021	2078
Sushi/CCP	PF00084	2083	2141
Sushi/CCP	PF00084	2146	2199
Sushi/CCP	PF00084	2204	2259
Sushi/CCP	PF00084	2264	2318
Sushi/CCP	PF00084	2323	2376
Sushi/CCP	PF00084	2381	2435
Sushi/CCP	PF00084	2440	2493
Sushi/CCP	PF00084	2498	2551
Sushi/CCP	PF00084	2556	2608
Sushi/CCP	PF00084	2660	2712
Sushi/CCP	PF00084	2717	2770
Sushi/CCP	PF00084	2775	2828
Sushi/CCP	PF00084	2833	2886
Sushi/CCP	PF00084	2891	2944
Sushi/CCP	PF00084	2949	3002
Sushi/CCP	PF00084	3007	3059
Sushi/CCP	PF00084	3064	3117
Sushi/CCP	PF00084	3122	3176
Sushi/CCP	PF00084	3181	3236
Sushi/CCP	PF00084	3241	3294
Sushi/CCP	PF00084	3299	3352
Sushi/CCP	PF00084	3357	3411
Sushi/CCP	PF00084	3416	3468

EGF-like	PF00008	3468	3499
EGF-like	PF00008	3504	3531
EGF-like	PF00008	3536	3563

5 Table 3. Relative expression of CNGH0004 in 82 human tissues *

Human RNA	Hs00295944	Hs00225829
Adrenal, Female, Adult	10.03	8.38
Aorta, Female, Fetal	1.00	1.00
Bladder, Male, Adult	6.77	5.27
Bladder, Diseased, Male, Adult	1.42	0.51
Bladder, Female, Fetal	11.07	9.16
Bladder, Male, Fetal	9.54	7.75
Brain, Female, Fetal	1.85	1.39
Brain, Male, Adult	2.38	1.79
Brain, Male, Fetal	0.87	0.95
Brain, Occipital Cortex, Male, Adult	2.78	2.43
Brain, Parietal Cortex, Male, Adult	2.08	2.05
Breast, Female, Adult	6.02	4.89
Caval Vein, Male, Adult	7.86	6.16
Cervix, Female, Adult	6.30	5.13
Colon, Female, Adult (Top)	57.59	54.30
Colon, Ascending, Female, Adult	7.68	5.97
Colon, Descending, Female, Adult	6.26	5.10
Colon, Normal, Male, Adult (Matched Set)	5.46	4.44
Colon, Diseased, Male, Adult (Matched Set)	5.48	4.62
Colon, Female, Fetal	9.62	7.86
Colon, Male, Adult	4.57	3.46
Colon, Male, Adult (Normal)	7.15	5.95
Colon, Male, Adult (Diseased)	4.98	4.13
Colon, Male, Fetal	8.78	6.81
Heart, Female, Adult	1.65	1.61
Heart, Female, Fetal	5.91	4.83
Heart, Left Atrium, Male, Adult	2.53	2.26
Heart, Male, Adult	3.59	3.26
Ileum, Diseased, Male, Adult	3.07	2.17
Ileum, Diseased, Male, Adult (Matched Set)	3.45	2.52
Ileum, Diseased, Male, Adult (Matched Set)	2.88	1.86
Kidney, Female, Fetal	4.42	3.28
Kidney, Diseased, Female, Adult (Matched Set)	8.34	6.60
Kidney, Diseased, Female, Adult (Matched Set)	3.91	3.60
Kidney, Female, Adult	7.48	5.65
Kidney, Male, Adult	1.28	0.98
Kidney, Male, Fetal	7.10	5.89
Larynx, Diseased, Male, Adult (Matched Set)	4.74	3.67
Larynx, Diseased, Male, Adult (Matched Set)	2.66	0.91
Larynx, Male, Adult	5.52	4.38
Larynx, Male, Adult	2.84	0.92
Larynx, Male, Adult (Normal)	9.50	7.67
Liver, Female, Adult	0.91	0.61
Liver, Female, Fetal	1.44	1.19
Liver, Male, Adult	3.75	3.03

Liver, Male, Fetal	1.69	1.36
Lung, Female, Adult	17.53	14.73
Lung, Female, Fetal	3.14	3.04
Lung, Male, Adult	11.47	9.77
Lung, Male, Fetal	8.69	7.67
Lymph Node, Male, Adult	2.33	1.79
Ovary, Female, Adult	23.13	17.83
Pancreas, Male, Adult	3.58	3.34
Parotid, Female, Adult	0.86	0.70
Penis, Male, Adult	8.64	6.83
Pericardium, Male, Adult	20.82	17.52
Placenta, Adult, Female	301.40	312.48
Prostate, Male, Adult	0.70	0.49
Rectum, Male, Adult	4.45	3.24
Skeletal Muscle, Female, Fetal	9.23	7.83
Skeletal Muscle, Male, Adult	6.32	5.32
Skeletal Muscle, Male, Fetal	9.57	8.85
Skin, Female, Adult	4.58	3.77
Skin, Female, Fetal	16.90	14.71
Skin, Male, Adult	28.13	23.60
Spleen, Female, Adult	5.82	4.61
Spleen, Female/Male pooled, Fetal	20.46	18.03
Spleen, Male, Adult	8.03	6.06
Stomach, Diseased, Female, Adult (Matched Set)	4.42	3.58
Stomach, Diseased, Female, Adult (Matched Set)	7.31	5.46
Stomach, Female, Adult	1.76	1.59
Stomach, Female, Fetal	13.89	10.74
Stomach, Male, Adult	3.12	2.12
Stomach, Male, Fetal	10.54	8.70
Testes, Male, Adult	14.52	12.14
Thymus, Male and Female, Fetal	1.21	0.89
Thymus, Male, Adult	15.42	12.14
Thyroid, Female, Adult	5.45	4.17
Tongue, Male/Female, Adult	7.27	5.91
Trachea, Female, Adult	5.90	4.60
Uterus, Female, Adult	7.94	5.72
Vulva, Diseased, Female, Adult	1.51	0.71

5

* Relative expression is calculated using a formula according to manufacturer's instruction (User Bulletin #2: ABI PRISM 7700 Sequence Detection System, Applied Biosystems, Foster City, CA). Evaluation of the copy number of mRNA of our gene of interest, CNGH0004, in specific tissues examined as shown in the table was compared with that of a calibrator tissue, in this case, Female Fetal

1.0 Aorta.

5 It will be clear that the invention can be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

10 **References**

1. Koo JY. Current consensus and update on psoriasis therapy: a perspective from the U.S. *J Dermatol* 1999; 26: 723-733.
2. Kapp A, Kemper A, Schopf E, Dercher H. Detection of circulating immune complexes in patients with atopic dermatitis and psoriasis. *Acta Derm Venerol* 1986; 66:121-126.
3. Kapp A, Schopf E. Cellular reactivity of polymorphonuclear leukocytes in psoriasis and atopic dermatitis. *Acta Derm Venerol* 1986; 66: 285-289.
4. Baadsgard O, Fisher GJ, Vorhees JJ, Cooper KD. The role of the immune system in the pathogenesis of psoriasis. *J Invest Dermatol* 1990; 5: 32S-34S.
5. Cooper KD. Psoriasis: Leukocytes ans cytokines. *Dermatol Clin* 1990; 8: 737-745.
6. Bowcock AM, Shannon W, Du FH, Duncan J, Cao K, Aftergut K, Catier J, Fernandez-Vina MA, Menter A. Insights into psoriasis and other inflammatory diseases from large-scale gene expression studies. *Hum Molec Genet* 2001; 10:1793-1805.
7. Oestreicher JL, Walters IB, Kikuchi T, Gilleaud P, Surette J, Schwertschlag U, Dorner AJ, Krueger JG, Trepicchio WL. Molecular classification of psoriasis disease-associated genes through pharmacogenomic expression profiling. *The Pharmacogenomics J* 2001; 1:272-287.
8. Cunningham MJ. Genomics and proteomics: The new millennium of drug discovery and development. *J Pharm Tox Methods* 2000; 44:291-300.
9. Salunga RG, Guo H, Luo L, Bittner A, Joy KC, Chambers J, Wan J, Jackson MR, Erlander MG. Gene expression analysis via cDNA microarray of laser capture microdissected cells from fixed tissue. In M. Schena (Ed.), *DNA microarrays a practical approach*, Oxford University Press, Oxford, 1999.
10. Gilges D, Vinit MA, Callebaut I, Coulombel L, Cacheux V, Romeo PH, Vigon I. Polydom: a secreted protein with pentraxin, complement control protein, epidermal growth factor and von Willebrand factor A domains. *Biochem J* 2000 Nov 15;352 Pt 1:49-59
11. Pucillo CE, Colombatti A, Vitale M, Salzano S, Rossi G, Formisano S. Type A modules: interacting domains found in several non-fibrillar collagens and in other extracellular matrix proteins. *Matrix*. 1993 Jul;13(4):297-306.

- 5 12. Campbell RD, Law SK, Reid KB, Sim RB. Structure, organization, and regulation of the complement genes. *Annu Rev Immunol.* 1988;6:161-95.
13. Reid KB and Day AJ. Structure-function relationships of the complement components. *Immunol Today.* 1989 Jun;10(6):177-80.
14. Kansas GS. Selectins and their ligands: current concepts and controversies. *Blood.* 1996 Nov 10 1;88(9):3259-87.
15. Wessel GM, Berg L, Adelson DL, Cannon G, McClay DR. A molecular analysis of hyalin--a substrate for cell adhesion in the hyaline layer of the sea urchin embryo. *Dev Biol.* 1998 Jan 15;193(2):115-26.
16. Bork P, Downing AK, Kieffer B, Campbell ID. Structure and distribution of modules in extracellular proteins. *Q Rev Biophys.* 1996 May;29(2):119-67.
17. Davis CG. The many faces of epidermal growth factor repeats. *New Biol.* 1990 May;2(5):410-9.
18. Gewurz H, Zhang XH, Lint TF. Structure and function of the pentraxins. *Curr Opin Immunol.* 1995 Feb;7(1):54-64.
19. Pinhaasov A., Amato FA, Kauffman J, Xin H, Brenneman D, Andrade-Gordon P and Ilyin SE.
20 High throughput TaqMan real time PCR assay for neuroscience applications. In press. *Journal of Neuroscience Methods.* 2003.

5 WHAT IS CLAIMED IS:

1. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide comprising or complementary to all of the contiguous nucleic acids 1001-11713 of SEQ ID NO:1.
2. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide comprising or complementary to at least 45 contiguous nucleotides 1001-11713 of SEQ ID NO:1.
3. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide encoding the amino acid sequence of SEQ ID NO:2, or a polynucleotide complementary thereto.
4. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide having at least 95-99% identity to a nucleotide sequence comprising or complementary to all of the contiguous nucleotides 1001-11713 of SEQ ID NO:1.
5. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide having at least 95-99% identity to a nucleotide sequence comprising or complementary to at least 45 of the contiguous nucleotides 1001-11713 of SEQ ID NO:1.
6. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide that hybridizes under stringent conditions to all of the contiguous nucleotides of SEQ ID NO:1 or a polynucleotide complementary thereto.
7. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide that hybridizes under stringent conditions to at least 45 contiguous nucleotides of SEQ ID NO:1 or a polynucleotide complementary thereto.
8. At least one CNGH0004 polypeptide, comprising all of the contiguous amino acids of SEQ ID NO:2.
9. At least one CNGH0004 polypeptide, comprising at least 15 contiguous amino acids of SEQ ID NO:2.
10. At least one CNGH0004 polypeptide, comprising at least one domain of SEQ ID NO:2.
11. At least one CNGH0004 polypeptide, comprising at least one polypeptide having at least 90-99% identity to an amino acid sequence comprising all of the contiguous amino acids of SEQ ID NO:2.
12. At least one CNGH0004 polypeptide, comprising at least one polypeptide having at least 90-99% identity to an amino acid sequence comprising at least 15 of the

5 contiguous amino acids of SEQ ID NO:2.

13. At least one CNGH0004 polypeptide, comprising at least one polypeptide encoded by at least one polynucleotide that hybridizes under stringent conditions to all of the contiguous nucleotides SEQ ID NO:1 or a polynucleotide complementary thereto.

14. At least one CNGH0004 polypeptide, comprising at least one polypeptide encoded by at least one polynucleotide that hybridizes under stringent conditions to at least 45 of the contiguous nucleotides SEQ ID NO:1 or a polynucleotide complementary thereto.

15. At least one CNGH0004 polypeptide, comprising at least one of 1-82, 83-259, 259-377, 378-433, 434-438, 438-493, 498-559, 1631-1685, 1690-1743, 1789-1842, 2021-2078, 2083-2141, 2146-2199, 2204-2259, 2264-2318, 2323-2376, 2381-2435, 2440-2493, 2498-2551, 2556-2608, 2660-2712, 2717-2770, 2775-2828, 2833-2886, 2891-2944, 2949-3002, 3007-3059, 3064-3117, 3122-3176, 3181-3236, 3241-3294, 3299-3352, 3357-3411, 3416-3468, 1231-1267, 1269-1305, 1307-1343, 1345-1381, 1383-1419, 1748-1784, 3468-3499, 3504-3531, 3536-3563, 1431-1623, 643-722, 561-642, 1196-1229, 727-787, 1847-1900, 1963-2016, 1905-1958, 999-1036, 1041-1106, 1108-1160, 1-41, or 305-360 of SEQ ID NO:1.

16. A CNGH0004 nucleic acid or CNGH0004 polypeptide according to any of claims 1-15, wherein said polypeptide has at least one activity of at least one CNGH0004 polypeptide.

17. A CNGH0004 antibody, comprising a monoclonal or polyclonal antibody, fusion protein, or fragment thereof, that specifically binds at least one CNGH0004 polypeptide according to any of claims 1-15.

18. A CNGH0004 nucleic acid encoding at least one CNGH0004 polypeptide or CNGH0004 antibody according to any of claim 1-17.

19. A CNGH0004 vector comprising at least one isolated nucleic acid according to any of claims 1-7.

20. A CNGH0004 host cell comprising an isolated nucleic acid according to claim 18.

21. A CNGH0004 host cell according to claim 20, wherein said host cell is at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, NSO, DG44 CHO, CHO K1, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof.

22. A method for producing at least one CNGH0004 polypeptide or CNGH0004 antibody, comprising translating a nucleic acid according to claim 18 under conditions in

5 vitro, in vivo or in situ, such that the CNGH0004 polypeptide is expressed in detectable or recoverable amounts.

23. A composition comprising at least one CNGH0004 nucleic acid, CNGH0004 polypeptide, or CNGH0004 antibody according to any of claims 1-17.

10 24. A composition according to claim 23, wherein said composition further comprises at least one pharmaceutically acceptable carrier or diluent.

15 25. A composition according to claim 23, further comprising at least one composition comprising an therapeutically effective amount of at least one compound, composition or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

20 26. A composition according to claim 23, in a form of at least one selected from a liquid, gas, or dry, solution, mixture, suspension, emulsion or colloid, a lyophilized preparation, a powder.

25 27. A method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

30 (a) contacting or administering a composition comprising an effective amount of at least one CNGH0004 nucleic acid, polypeptide or antibody according to any of claims 1-17, with, or to, said cell, tissue, organ or animal.

35 28. A method according to claim 27, wherein said effective amount is 0.001-50 mg of CNGH0004 antibody; 0.000001-500 mg of said CNGH0004 polypeptide; or 0.0001-100 μ g of said CNGH0004 nucleic acid per kilogram of said cells, tissue, organ or animal.

30 29. A method according to claim 27, wherein said contacting or said administrating is by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

5 30. A method according to claim 27, further comprising administering, prior, concurrently or after said (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a
10 gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

15 31. A device, comprising at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17, wherein said device is suitable for contacting or administering said at least one of said CNGH0004 polypeptide, antibody or nucleic acid, by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, 20 intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

25 32. An article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17.

30 33. The article of manufacture of claim 32, wherein said container is a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

35 34. A method for producing at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17, comprising providing at least one host cell, transgenic animal, transgenic plant, plant cell capable of expressing in detectable or recoverable amounts said polypeptide, antibody or nucleic acid.

- 5 35. At least one CNGH0004 polypeptide, antibody or nucleic acid,
produced by a method according to claim 34.

5 SEQUENCE LISTING

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25	630 635 640 645 gaa cca cct gtc ata gac tgg tgc aga tct cca cct ccc gtc cag gtc Glu Pro Pro Val Ile Asp Trp Cys Arg Ser Pro Pro Pro Val Gln Val 650 655 660	2983
	tcg gag aag gta cat gcc gca agc tgg gat gag cct cag ttc tca gac Ser Glu Lys Val His Ala Ala Ser Trp Asp Glu Pro Gln Phe Ser Asp 665 670 675	3031
30	aac tca ggg gct gaa ttg gtc att acc aga agt cat aca caa gga gac Asn Ser Gly Ala Glu Leu Val Ile Thr Arg Ser His Thr Gln Gly Asp 680 685 690	3079
	ctt ttc cct caa ggg gag act ata gta cag tat aca gcc act gac ccc Leu Phe Pro Gln Gly Glu Thr Ile Val Gln Tyr Thr Ala Thr Asp Pro 695 700 705	3127
35	tca ggc aat aac agg aca tgt gat atc cat att gtc ata aaa ggt tct Ser Gly Asn Asn Arg Thr Cys Asp Ile His Ile Val Ile Lys Gly Ser	3175
	710 715 720 725 ccc tgt gaa att cca ttc aca cct gta aat ggg gat ttt ata tgc act Pro Cys Glu Ile Pro Phe Thr Pro Val Asn Gly Asp Phe Ile Cys Thr 730 735 740	3223
40	cca gat aat act gga gtc aac tgt aca tta act tgc ttg gag ggc tat Pro Asp Asn Thr Gly Val Asn Cys Thr Leu Thr Cys Leu Glu Gly Tyr 745 750 755	3271
	gat ttc aca gaa ggg tct act gac aag tat tat tgt gct tat gaa gat Asp Phe Thr Glu Gly Ser Thr Asp Lys Tyr Tyr Cys Ala Tyr Glu Asp 760 765 770	3319

5	ggc gtc tgg aaa cca aca tat acc act gaa tgg cca gac tgt gcc aaa Gly Val Trp Lys Pro Thr Tyr Thr Glu Trp Pro Asp Cys Ala Lys 775 780 785	3367
	aaa cgt ttt gca aac cac ggg ttc aag tcc ttt gag atg ttc tac aaa Lys Arg Phe Ala Asn His Gly Phe Lys Ser Phe Glu Met Phe Tyr Lys	3415
10	790 795 800 805 gca gct cgt tgt gat gac aca gat ctg atg aag aag ttt tct gaa gca Ala Ala Arg Cys Asp Asp Thr Asp Leu Met Lys Lys Phe Ser Glu Ala 810 815 820	3463
	ttt gag acg acc ctg gga aaa atg gtc cca tca ttt tgt agt gat gca Phe Glu Thr Thr Leu Gly Lys Met Val Pro Ser Phe Cys Ser Asp Ala 825 830 835	3511
15	gag gac att gac tgc aga ctg gag gag aac ctg acc aaa aaa tat tgc Glu Asp Ile Asp Cys Arg Leu Glu Asn Leu Thr Lys Lys Tyr Cys 840 845 850	3559
	cta gaa tat aat tat gac tat gaa aat ggc ttt gca att gga cca ggt Leu Glu Tyr Asn Tyr Asp Tyr Glu Asn Gly Phe Ala Ile Gly Pro Gly 855 860 865	3607
20	ggc tgg ggt gca gct aat agg ctg gat tac tct tac gat gac ttc ctg Gly Trp Gly Ala Ala Asn Arg Leu Asp Tyr Ser Tyr Asp Asp Phe Leu 870 875 880 885	3655
	gac act gtg caa gaa aca gcc aca agc atc ggc aat gcc aag tcc tca Asp Thr Val Gln Glu Thr Ala Thr Ser Ile Gly Asn Ala Lys Ser Ser 890 895 900	3703
25	cgg att aaa aga agt gcc cca tta tct gac tat aaa att aag tta att Arg Ile Lys Arg Ser Ala Pro Leu Ser Asp Tyr Lys Ile Lys Leu Ile 905 910 915	3751
	ttt aac atc aca gct agt gtg cca tta ccc gat gaa aga aat gat acc Phe Asn Ile Thr Ala Ser Val Pro Leu Pro Asp Glu Arg Asn Asp Thr 920 925 930	3799
30	ctt gaa tgg gaa aat cag caa cga ctc ctt cag aca ttg gaa act atc Leu Glu Trp Glu Asn Gln Gln Arg Leu Leu Gln Thr Leu Glu Thr Ile 935 940 945	3847
	aca aat aaa ctg aaa agg act ctc aac aaa gac ccc atg tat tcc ttt Thr Asn Lys Leu Lys Arg Thr Leu Asn Lys Asp Pro Met Tyr Ser Phe 950 955 960 965	3895
35	cag ctt gca tca gaa ata ctt ata gcc gac agc aat tca tta gaa aca Gln Leu Ala Ser Glu Ile Leu Ile Ala Asp Ser Asn Ser Leu Glu Thr 970 975 980	3943
	aaa aag gct tcc ccc ttc tgc aga cca ggc tca gtg ctg aga ggg cgt Lys Lys Ala Ser Pro Phe Cys Arg Pro Gly Ser Val Leu Arg Gly Arg 985 990 995	3991
40	atg tgt gtc aat tgc cct ttg gga acc tat tat aat ctg gaa cat Met Cys Val Asn Cys Pro Leu Gly Thr Tyr Tyr Asn Leu Glu His 1000 1005 1010	4036

5	ttc acc tgt gaa agc tgc cgg atc	gga tcc tat caa gat	gaa gaa	4081
	Phe Thr Cys Glu Ser Cys Arg Ile	Gly Ser Tyr Gln Asp	Glu Glu	
	1015	1020	1025	
	ggg caa ctt gag tgc aag ctt tgc	ccc tct ggg atg tac	acg gaa	4126
	Gly Gln Leu Glu Cys Lys. Leu Cys	Pro Ser Gly Met Tyr	Thr Glu	
10	1030	1035	1040	
	tat atc cat tca aga aac atc tct	gat tgt aaa gct cag	tgt aaa	4171
	Tyr Ile His Ser Arg Asn Ile Ser	Asp Cys Lys Ala Gln	Cys Lys	
	1045	1050	1055	
	caa ggc acc tac tca tac agt gga	ctt gag act tgt gaa	tgc tgt	4216
15	Gln Gly Thr Tyr Ser Tyr Ser Gly	Leu Glu Thr Cys Glu	Ser Cys	
	1060	1065	1070	
	cca ctg ggc act tat cag cca aaa	ttt ggt tcc cgg agc	tgc ctc	4261
	Pro Leu Gly Thr Tyr Gln Pro Lys	Phe Gly Ser Arg Ser	Cys Leu	
	1075	1080	1085	
20	tgc tgt cca gaa aac acc tca act	gtg aaa aga gga gcc	gtg aac	4306
	Ser Cys Pro Glu Asn Thr Ser Thr	Val Lys Arg Gly Ala	Val Asn	
	1090	1095	1100	
	att tct gca tgt gga gtt cct tgt	cca gaa gga aaa ttc	tgc cgt	4351
	Ile Ser Ala Cys Gly Val Pro Cys	Pro Glu Gly Lys Phe	Ser Arg	
25	1105	1110	1115	
	tct ggg tta atg ccc tgt cac cca	tgt cct cgt gac tat	tac caa	4396
	Ser Gly Leu Met Pro Cys His Pro	Cys Pro Arg Asp Tyr	Tyr Gln	
	1120	1125	1130	
	cct aat gca ggg aag gcc ttc tgc	ctg gcc tgt ccc ttt	tat gga	4441
30	Pro Asn Ala Gly Lys Ala Phe Cys	Leu Ala Cys Pro Phe	Tyr Gly	
	1135	1140	1145	
	act acc cca ttc gct ggt tcc aga	tcc atc aca gaa tgt	tca agt	4486
	Thr Thr Pro Phe Ala Gly Ser Arg	Ser Ile Thr Glu Cys	Ser Ser	
	1150	1155	1160	
35	ttt agt tca act ttc tca gcg gca	gag gaa agt gtg gtg	ccc cct	4531
	Phe Ser Ser Thr Phe Ser Ala Ala	Glu Glu Ser Val Val	Pro Pro	
	1165	1170	1175	
	gcc tct ctt gga cat att aaa aag	agg cat gaa atc agc	agt cag	4576
	Ala Ser Leu Gly His Ile Lys Lys	Arg His Glu Ile Ser	Ser Gln	
40	1180	1185	1190	
	gtt ttc cat gaa tgc ttc ttt aac	cct tgc cac aat agt	gga acc	4621
	Val Phe His Glu Cys Phe Phe Asn	Pro Cys His Asn Ser	Gly Thr	
	1195	1200	1205	
	tgc cag caa ctt ggg cgt ggt tat	gtt tgt ctc tgt cca	ctt gga	4666
45	Cys Gln Gln Leu Gly Arg Gly Tyr	Val Cys Leu Cys Pro	Leu Gly	
	1210	1215	1220	
	tat aca ggc tta aag tgt gaa aca	gac atc gat gag tgc	agc cca	4711
	Tyr Thr Gly Leu Lys Cys Glu Thr	Asp Ile Asp Glu Cys	Ser Pro	
	1225	1230	1235	

5	ctg cct tgc ctc aac aat gga gtt	tgt aaa gac cta gtt	ggg gaa	4756
	Leu Pro Cys Leu Asn Asn Gly Val	Cys Lys Asp Leu Val	Gly Glu	
	1240	1245	1250	
	tcc att tgt gag tgc cca tca ggt	tac aca ggt cag cgg	tgt gaa	4801
	Phe Ile Cys Glu Cys Pro Ser Gly	Tyr Thr Gly Gln Arg	Cys Glu	
10	1255	1260	1265	
	gaa aat ata aat gag tgt agc tcc	agt cct tgt tta aat	aaa gga	4846
	Glu Asn Ile Asn Glu Cys Ser Ser	Ser Pro Cys Leu Asn	Lys Gly	
	1270	1275	1280	
	atc tgt gtt gat ggt gtg gct ggc	tat cgt tgc aca tgt	gtg aaa	4891
15	Ile Cys Val Asp Gly Val Ala Gly	Tyr Arg Cys Thr Cys	Val Lys	
	1285	1290	1295	
	gga ttt gta ggc ctg cat tgt gaa	aca gaa gtc aat gaa	tgc cag	4936
	Gly Phe Val Gly Leu His Cys Glu	Thr Glu Val Asn Glu	Cys Gln	
	1300	1305	1310	
20	tca aac cca tgc tta aat aat gca	gtc tgt gaa gac cag	gtt ggg	4981
	Ser Asn Pro Cys Leu Asn Asn Ala	Val Cys Glu Asp Gln	Val Gly	
	1315	1320	1325	
	gga ttc ttg tgc aaa tgc cca cct	gga ttt ttg ggt acc	cga tgt	5026
	Gly Phe Leu Cys Lys Cys Pro Pro	Gly Phe Leu Gly Thr	Arg Cys	
25	1330	1335	1340	
	gga aag aac gtc gat gag tgt ctc	agt cag cca tgc aaa	aat gga	5071
	Gly Lys Asn Val Asp Glu Cys Leu	Ser Gln Pro Cys Lys	Asn Gly	
	1345	1350	1355	
	gct acc tgt aaa gac ggt gcc aat	agc ttc aga tgc ctg	tgt gca	5116
30	Ala Thr Cys Lys Asp Gly Ala Asn	Ser Phe Arg Cys Leu	Cys Ala	
	1360	1365	1370	
	gct ggc ttc aca gga tca cac tgt	gaa ttg aac atc aat	gaa tgt	5161
	Ala Gly Phe Thr Gly Ser His Cys	Glu Leu Asn Ile Asn	Glu Cys	
	1375	1380	1385	
35	cag tct aat cca tgt aga aat cag	gcc acc tgt gtg gat	gaa tta	5206
	Gln Ser Asn Pro Cys Arg Asn Gln	Ala Thr Cys Val Asp	Glu Leu	
	1390	1395	1400	
	aat tca tac agt tgt aaa tgt cag	cca gga ttt tca ggc	aaa agg	5251
	Asn Ser Tyr Ser Cys Lys Cys Gln	Pro Gly Phe Ser Gly	Lys Arg	
40	1405	1410	1415	
	tgt gaa aca gaa cag tct aca ggc	ttt aac ctg gat ttt	gaa gtt	5296
	Cys Glu Thr Glu Gln Ser Thr Gly	Phe Asn Leu Asp Phe	Glu Val	
	1420	1425	1430	
	tct ggc atc tat gga tat gtc atg	cta gat ggc atg ctc	cca tct	5341
45	Ser Gly Ile Tyr Gly Tyr Val Met	Leu Asp Gly Met Leu	Pro Ser	
	1435	1440	1445	
	ctc cat gct cta acc tgt acc ttc	tgg atg aaa tcc tct	gac gac	5386
	Leu His Ala Leu Thr Cys Thr Phe	Trp Met Lys Ser Ser	Asp Asp	
	1450	1455	1460	

5	atg aac tat gga aca cca atc tcc	tat gca gtt gat aac ggc agc	5431
	Met Asn Tyr Gly Thr Pro Ile Ser	Tyr Ala Val Asp Asn Gly Ser	
	1465 1470	1475	
	gac aat acc ttg ctc ctg act gat	tat aac ggc tgg gtt ctt tat	5476
	Asp Asn Thr Leu Leu Leu Thr Asp	Tyr Asn Gly Trp Val Leu Tyr	
10	1480	1485	1490
	gtg aat ggc agg gaa aag ata aca	aac tgt ccc tcg gtg aat gat	5521
	Val Asn Gly Arg Glu Lys Ile Thr	Asn Cys Pro Ser Val Asn Asp	
	1495 1500	1505	
	ggc aga tgg cat cat att gca atc	act tgg aca agt gcc aat ggc	5566
15	Gly Arg Trp His His Ile Ala Ile	Thr Trp Thr Ser Ala Asn Gly	
	1510 1515	1520	
	atc tgg aaa gtc tat atc gat ggg	aaa tta tct gac ggt ggt gct	5611
	Ile Trp Lys Val Tyr Ile Asp Gly	Lys Leu Ser Asp Gly Gly Ala	
	1525 1530	1535	
20	ggc ctc tct gtt ggt ttg ccc ata	cct ggt ggt ggt gcg tta gtt	5656
	Gly Leu Ser Val Gly Leu Pro Ile	Pro Gly Gly Ala Leu Val	
	1540 1545	1550	
	ctg ggg caa gag caa gac aaa aaa	gga gag gga ttc agc cca gct	5701
	Leu Gly Gln Glu Gln Asp Lys Lys	Gly Glu Gly Phe Ser Pro Ala	
25	1555 1560	1565	
	gag tct ttt gtg ggc tcc ata agc	cag ctc aac ctc tgg gac tat	5746
	Glu Ser Phe Val Gly Ser Ile Ser	Gln Leu Asn Leu Trp Asp Tyr	
	1570 1575	1580	
	gtc ctg tct cca cag cag gtg aag	tca ctg gct acc tcc tgc cca	5791
30	Val Leu Ser Pro Gln Gln Val Lys	Ser Leu Ala Thr Ser Cys Pro	
	1585 1590	1595	
	gag gaa ctc agt aaa gga aac gtg	tta gca tgg cct gat ttc ttg	5836
	Glu Glu Leu Ser Lys Gly Asn Val	Leu Ala Trp Pro Asp Phe Leu	
	1600 1605	1610	
35	tca gga att gtg ggg aaa gtg aag	atc gat tct aag agc ata ttt	5881
	Ser Gly Ile Val Gly Lys Val Lys	Ile Asp Ser Lys Ser Ile Phe	
	1615 1620	1625	
	tgt tct gat tgc cca cgc tta gga	ggg tca gtg cct cat ctg aga	5926
	Cys Ser Asp Cys Pro Arg Leu Gly	Gly Ser Val Pro His Leu Arg	
40	1630 1635	1640	
	act gca tct gaa gat tta aag cca	ggt tcc aaa gtc aat ctg ttc	5971
	Thr Ala Ser Glu Asp Leu Lys Pro	Gly Ser Lys Val Asn Leu Phe	
	1645 1650	1655	
	tgt gat cca ggc ttc cag ctg gtc	ggg aac cct gtg cag tac tgt	6016
45	Cys Asp Pro Gly Phe Gln Leu Val	Gly Asn Pro Val Gln Tyr Cys	
	1660 1665	1670	
	ctg aat caa gga cag tgg aca caa	cca ctt cct cac tgt gaa cgc	6061
	Leu Asn Gln Gly Gln Trp Thr Gln	Pro Leu Pro His Cys Glu Arg	
	1675 1680	1685	

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5	att agc tgt ggg gtg cca cct cct ttg gag aat ggc ttc cat tca		6106
	Ile Ser Cys Gly Val Pro Pro Pro Leu Glu Asn Gly Phe His Ser		
	1690 1695 1700		
	gcc gat gac ttc tat gct ggc agc aca gta acc tac cag tgc aac		6151
	Ala Asp Asp Phe Tyr Ala Gly Ser Thr Val Thr Tyr Gln Cys Asn		
10	1705 1710 1715		
	aat ggc tac tat cta ttg ggt gac tca agg atg ttc tgt aca gat		6196
	Asn Gly Tyr Tyr Leu Leu Gly Asp Ser Arg Met Phe Cys Thr Asp		
	1720 1725 1730		
	aat ggg agc tgg aac ggc gtt tca cca tcc tgc ctt gat gtc gat		6241
15	Asn Gly Ser Trp Asn Gly Val Ser Pro Ser Cys Leu Asp Val Asp		
	1735 1740 1745		
	gag tgt gca gtt gga tca gat tgt agt gag cat gct tct tgc ctg		6286
	Glu Cys Ala Val Gly Ser Asp Cys Ser Glu His Ala Ser Cys Leu		
	1750 1755 1760		
20	aac gta gat gga tcc tac ata tgt tca tgt gtc cca ccg tac aca		6331
	Asn Val Asp Gly Ser Tyr Ile Cys Ser Cys Val Pro Pro Tyr Thr		
	1765 1770 1775		
	gga gat ggg aaa aac tgt gca gaa cct ata aaa tgt aag gct cca		6376
	Gly Asp Gly Lys Asn Cys Ala Glu Pro Ile Lys Cys Lys Ala Pro		
25	1780 1785 1790		
	gga aat ccg gaa aat ggc cac tcc tca ggt gag att tat aca gta		6421
	Gly Asn Pro Glu Asn Gly His Ser Ser Gly Glu Ile Tyr Thr Val		
	1795 1800 1805		
	ggt gcc gca gtc aca ttt tcg tgt cag gaa gga tac cag ttg atg		6466
30	Gly Ala Ala Val Thr Phe Ser Cys Gln Glu Gly Tyr Gln Leu Met		
	1810 1815 1820		
	gga gta acc aaa atc aca tgt ttg gag tct gga gaa tgg aat cat		6511
	Gly Val Thr Lys Ile Thr Cys Leu Glu Ser Gly Glu Trp Asn His		
	1825 1830 1835		
35	cta ata cca tat tgt aaa gct gtt tca tgt ggt aaa ccg gct att		6556
	Leu Ile Pro Tyr Cys Lys Ala Val Ser Cys Gly Lys Pro Ala Ile		
	1840 1845 1850		
	cca gaa aat ggt tgc att gag gag tta gca ttt act ttt ggc agc		6601
	Pro Glu Asn Gly Cys Ile Glu Glu Leu Ala Phe Thr Phe Gly Ser		
40	1855 1860 1865		
	aaa gtg aca tat agg tgt aat aaa gga tat act ctg gcc ggt gat		6646
	Lys Val Thr Tyr Arg Cys Asn Lys Gly Tyr Thr Leu Ala Gly Asp		
	1870 1875 1880		
	aaa gaa tca tcc tgt ctt gct aac agt tct tgg agt cat tcc cct		6691
45	Lys Glu Ser Ser Cys Leu Ala Asn Ser Ser Trp Ser His Ser Pro		
	1885 1890 1895		
	cct gtg tgt gaa cca gtg aag tgt tct agt ccg gaa aat ata aat		6736
	Pro Val Cys Glu Pro Val Lys Cys Ser Ser Pro Glu Asn Ile Asn		
	1900 1905 1910		

5	aat gga aaa tat att ttg agt ggg ctt acc tac ctt tct act gca	6781
	Asn Gly Lys Tyr Ile Leu Ser Gly Leu Thr Tyr Leu Ser Thr Ala	
	1915 1920 1925	
	tca tat tca tgc gat aca gga tac agc tta cag ggc cct tcc att	6826
	Ser Tyr Ser Cys Asp Thr Gly Tyr Ser Leu Gln Gly Pro Ser Ile	
10	1930 1935 1940	
	att gaa tgc acg gct tct ggc atc tgg gac aga gcg cca cct gcc	6871
	Ile Glu Cys Thr Ala Ser Gly Ile Trp Asp Arg Ala Pro Pro Ala	
	1945 1950 1955	
	tgt cac ctc gtc ttc tgt gga gaa cca cct gcc atc aaa gat gct	6916
15	Cys His Leu Val Phe Cys Gly Glu Pro Pro Ala Ile Lys Asp Ala	
	1960 1965 1970	
	gtc att acg ggg aat aac ttc act ttc agg aac acc gtc act tac	6961
	Val Ile Thr Gly Asn Asn Phe Thr Phe Arg Asn Thr Val Thr Tyr	
	1975 1980 1985	
20	act tgc aaa gaa ggc tat act ctt gct ggt ctt gac acc att gaa	7006
	Thr Cys Lys Glu Gly Tyr Thr Leu Ala Gly Leu Asp Thr Ile Glu	
	1990 1995 2000	
	tgc ctg gcc gac ggc aag tgg agt aga agt gac cag cag tgc ctg	7051
	Cys Leu Ala Asp Gly Lys Trp Ser Arg Ser Asp Gln Gln Cys Leu	
25	2005 2010 2015	
	gct gtc tcc tgt gat gag cca ccc att gtg gac cac gcc tct cca	7096
	Ala Val Ser Cys Asp Glu Pro Pro Ile Val Asp His Ala Ser Pro	
	2020 2025 2030	
	gag act gcc cat cgg ctc ttt gga gac att gca ttc tac tac tgc	7141
30	Glu Thr Ala His Arg Leu Phe Gly Asp Ile Ala Phe Tyr Tyr Cys	
	2035 2040 2045	
	tct gat ggt tac agc cta gca gac aat tcc cag ctt ctc tgc aat	7186
	Ser Asp Gly Tyr Ser Leu Ala Asp Asn Ser Gln Leu Leu Cys Asn	
	2050 2055 2060	
35	gcc cag ggc aag tgg gta ccc cca gaa ggt caa gac atg ccc cgt	7231
	Ala Gln Gly Lys Trp Val Pro Pro Glu Gly Gln Asp Met Pro Arg	
	2065 2070 2075	
	tgt ata gct cat ttc tgt gaa aaa cct cca tcg gtt tcc tat agc	7276
	Cys Ile Ala His Phe Cys Glu Lys Pro Pro Ser Val Ser Tyr Ser	
40	2080 2085 2090	
	atc ttg gaa tct gtg agc aaa gca aaa ttt gca gct ggc tca gtt	7321
	Ile Leu Glu Ser Val Ser Lys Ala Lys Phe Ala Ala Gly Ser Val	
	2095 2100 2105	
	gtg agc ttt aaa tgc atg gaa ggc ttt gta ctg aac acc tca gca	7366
45	Val Ser Phe Lys Cys Met Glu Gly Phe Val Leu Asn Thr Ser Ala	
	2110 2115 2120	
	aag att gaa tgt atg aga ggt ggg cag tgg aac cct tcc ccc atg	7411
	Lys Ile Glu Cys Met Arg Gly Gly Gln Trp Asn Pro Ser Pro Met	
	2125 2130 2135	

5	tcc atc cag tgc atc cct gtg cggttgt gga gag cca cca agc atc Ser Ile Gln Cys Ile Pro Val Arg Cys Gly Glu Pro Pro Ser Ile 2140 2145 2150	7456
	atg aat ggc tat gca agt gga tca aac tac agt ttt gga gcc atg Met Asn Gly Tyr Ala Ser Gly Ser Asn Tyr Ser Phe Gly Ala Met 10 2155 2160 2165	7501
	gtg gct tac agc tgc aac aag ggg ttc tac atc aaa ggg gaa aag Val Ala Tyr Ser Cys Asn Lys Gly Phe Tyr Ile Lys Gly Glu Lys 2170 2175 2180	7546
15	aag agc acc tgc gaa gcc aca ggg cag tgg agt agt cct ata ccg Lys Ser Thr Cys Glu Ala Thr Gly Gln Trp Ser Ser Pro Ile Pro 2185 2190 2195	7591
	acg tgc cac ccg gta tct tgt ggt gaa cca cct aag gtt gag aat Thr Cys His Pro Val Ser Cys Gly Glu Pro Pro Lys Val Glu Asn 2200 2205 2210	7636
20	ggc ttt ctg gag cat aca act ggc agg atc ttt gag agt gaa gtg Gly Phe Leu Glu His Thr Thr Gly Arg Ile Phe Glu Ser Glu Val 2215 2220 2225	7681
	agg tat cag tgt aac ccg ggc tat aag tca gtc gga agt cct gta Arg Tyr Gln Cys Asn Pro Gly Tyr Lys Ser Val Gly Ser Pro Val 2230 2235 2240	7726
25	ttt gtc tgc caa gcc aat cgc cac tgg cac agt gaa tcc cct ctg Phe Val Cys Gln Ala Asn Arg His Trp His Ser Glu Ser Pro Leu 2245 2250 2255	7771
	atg tgt gtt cct ctc gac tgt gga aaa cct ccc ccg atc cag aat 30 Met Cys Val Pro Leu Asp Cys Gly Lys Pro Pro Pro Ile Gln Asn 2260 2265 2270	7816
	ggc ttc atg aaa gga gaa aac ttt gaa gta ggg tcc aag gtt cag Gly Phe Met Lys Gly Glu Asn Phe Glu Val Gly Ser Lys Val Gln 2275 2280 2285	7861
35	ttt ttc tgt aat gag ggt tat gag ctt gtt ggt gac agt tct tgg Phe Phe Cys Asn Glu Gly Tyr Glu Leu Val Gly Asp Ser Ser Trp 2290 2295 2300	7906
	aca tgt cag aaa tct ggc aaa tgg aat aag aag tca aat cca aag Thr Cys Gln Lys Ser Gly Lys Trp Asn Lys Lys Ser Asn Pro Lys 40 2305 2310 2315	7951
	tgc atg cct gcc aag tgc cca gag ccg ccc ctc ttg gaa aac cag Cys Met Pro Ala Lys Cys Pro Glu Pro Pro Leu Leu Glu Asn Gln 2320 2325 2330	7996
45	cta gta tta aag gag ttg acc acc gag gta gga gtt gtg aca ttt Leu Val Leu Lys Glu Leu Thr Thr Glu Val Gly Val Val Thr Phe 2335 2340 2345	8041
	tcc tgt aaa gaa ggg cat gtc ctg caa ggc ccc tct gtc ctg aaa Ser Cys Lys Glu Gly His Val Leu Gln Gly Pro Ser Val Leu Lys 2350 2355 2360	8086

5	tgc ttg cca	tcc cag caa tgg aat	gac tct ttc cct gtt	tgt aag	8131
	Cys Leu Pro	Ser Gln Gln Trp Asn	Asp Ser Phe Pro Val	Cys Lys	
	2365	2370	2375		
	att gtt ctt	tgt acc cca cct ccc	cta att tcc ttt ggt	gtc ccc	8176
	Ile Val Leu	Cys Thr Pro Pro Pro	Leu Ile Ser Phe Gly	Val Pro	
10	2380	2385	2390		
	att cct tct	tct gct ctt cat ttt	gga agt act gtc aag	tat tct	8221
	Ile Pro Ser	Ser Ala Leu His Phe	Gly Ser Thr Val Lys	Tyr Ser	
	2395	2400	2405		
	tgt gta ggt	ggg ttt ttc cta aga	gga aat tct acc acc	ctc tgc	8266
15	Cys Val Gly	Gly Phe Phe Leu Arg	Gly Asn Ser Thr Thr	Leu Cys	
	2410	2415	2420		
	caa cct gat	ggc acc tgg agc tct	cca ctg cca gaa tgt	gtt cca	8311
	Gln Pro Asp	Gly Thr Trp Ser Ser	Pro Leu Pro Glu Cys	Val Pro	
	2425	2430	2435		
20	gta gaa tgt	ccc caa cct gag gaa	atc ccc aat gga atc	att gat	8356
	Val Glu Cys	Pro Gln Pro Glu Glu	Ile Pro Asn Gly Ile	Ile Asp	
	2440	2445	2450		
	gtg caa ggc	ctt gcc tat ctc agc	aca gct ctc tat acc	tgc aag	8401
	Val Gln Gly	Leu Ala Tyr Leu Ser	Thr Ala Leu Tyr Thr	Cys Lys	
25	2455	2460	2465		
	cca ggc ttt	gaa ttg gtg gga aat	act acc acc ctt tgt	gga gaa	8446
	Pro Gly Phe	Glu Leu Val Gly Asn	Thr Thr Thr Leu Cys	Gly Glu	
	2470	2475	2480		
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30	Asn Gly His	Trp Leu Gly Gly Lys	Pro Thr Cys Lys Ala	Ile Glu	
	2485	2490	2495		
	tgc ctg aaa	ccc aag gag att ttg	aat ggc aaa ttc tct	tac acg	8536
	Cys Leu Lys	Pro Lys Glu Ile Leu	Asn Gly Lys Phe Ser	Tyr Thr	
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35	gac cta cac	tat gga cag acc gtt	acc tac tct tgc aac	cga ggc	8581
	Asp Leu His	Tyr Gly Gln Thr Val	Thr Tyr Ser Cys Asn	Arg Gly	
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	ttt cgg ctc	gaa ggt ccc agt gcc	ttg acc tgt tta gag	aca ggt	8626
	Phe Arg Leu	Glu Gly Pro Ser Ala	Leu Thr Cys Leu Glu	Thr Gly	
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	gat tgg gat	gta gat gcc cca tct	tgc aat gcc atc cac	tgt gat	8671
	Asp Trp Asp	Val Asp Ala Pro Ser	Cys Asn Ala Ile His	Cys Asp	
	2545	2550	2555		
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45	Ser Pro Gln	Pro Ile Glu Asn Gly	Phe Val Glu Gly Ala	Asp Tyr	
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	agc tat ggt	gcc ata atc atc tac	agt tgc ttc cct ggg	ttt cag	8761
	Ser Tyr Gly	Ala Ile Ile Ile Tyr	Ser Cys Phe Pro Gly	Phe Gln	
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	Val Ala Gly His Ala Met Gln Thr	Cys Glu Glu Ser Gly	Trp Ser	
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	agt tcc atc cca aca tgt atg cca	ata gac tgt ggc ctc	cct cct	8851
	Ser Ser Ile Pro Thr Cys Met Pro	Ile Asp Cys Gly Leu	Pro Pro	
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	His Ile Asp Phe Gly Asp Cys Thr	Lys Leu Lys Asp Asp	Gln Gly	
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	Pro His Pro Pro Tyr His Leu Gly	Ala Val Ala Lys Thr	Trp Glu	
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	Asn Thr Lys Glu Ser Pro Ala Thr	His Ser Ser Asn Phe	Leu Tyr	
	2665	2670	2675	
	ggt acc atg gtt tca tac acc tgt	aat cca gga tat gaa	ctt ctg	9076
	Gly Thr Met Val Ser Tyr Thr Cys	Asn Pro Gly Tyr Glu	Leu Leu	
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	Gly Asn Pro Val Leu Ile Cys Gln	Glu Asp Gly Thr Trp	Asn Gly	
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	Pro Glu Asn Gly Phe Leu Arg Phe	Thr Glu Thr Ser Met	Gly Ser	
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	Ala Val Gln Tyr Ser Cys Lys Pro	Gly His Ile Leu Ala	Gly Ser	
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	Asp Leu Arg Leu Cys Leu Glu Asn	Arg Lys Trp Ser Gly	Ala Ser	
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	Pro Arg Cys Glu Ala Ile Ser Cys	Lys Lys Pro Asn Pro	Val Met	
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	Tyr Tyr Glu Cys Asp Pro Gly Tyr	Val Leu Asn Gly Thr	Glu Arg	
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	Arg Thr Gys Gln Asp Asp Lys Asn	Trp Asp Glu Asp Glu	Pro Ile	
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	Cys Ile Pro Val Asp Cys Ser Ser	Pro Pro Val Ser Ala	Asn Gly	
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	Gln Val Arg Gly Asp Glu Tyr Thr	Phe Gln Lys Glu Ile	Glu Tyr	
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	tgt ctt gcc aat gga agt tgg agt	gga gcc act ccc gac	tgt gtg	9661
	Cys Leu Ala Asn Gly Ser Trp Ser	Gly Ala Thr Pro Asp	Cys Val	
	2875	2880	2885	
20	cct gtc aga tgt gcc acc ccg cca	caa ctg gcc aat ggg	gtg acg	9706
	Pro Val Arg Cys Ala Thr Pro Pro	Gln Leu Ala Asn Gly	Val Thr	
	2890	2895	2900	
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	Glu Gly Leu Asp Tyr Gly Phe Met	Lys Glu Val Thr Phe	His Cys	
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	His Glu Gly Tyr Ile Leu His Gly	Ala Pro Lys Leu Thr	Cys Gln	
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	aac tgt gga cct cct gaa gat ctt	gcc cat ggt ttc cct	aat ggt	9886
	Asn Cys Gly Pro Pro Glu Asp Leu	Ala His Gly Phe Pro	Asn Gly	
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	Phe Ser Phe Ile His Gly Gly His	Ile Gln Tyr Gln Cys	Phe Pro	
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	Gly Tyr Lys Leu His Gly Asn Ser	Ser Arg Arg Cys Leu	Ser Asn	
40	2980	2985	2990	
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	Gly Ser Trp Ser Gly Ser Ser Pro	Ser Cys Leu Pro Cys	Arg Cys	
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	gac tgt gga aag gca gcc cgg att	cag tgc ttc aaa ggc	ttc aag	10111
	Asp Cys Gly Lys Ala Ala Arg Ile	Gln Cys Phe Lys Gly	Phe Lys	
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	agc tct ggg ttc ccc cac tgt gaa cac act tct tgt ggt tct ctt Ser Ser Gly Phe Pro His Cys Glu His Thr Ser Cys Gly Ser Leu	10201
10	cca atg ata cca aat gcg ttc atc agt gag acc agc tct tgg aag Pro Met Ile Pro Asn Ala Phe Ile Ser Glu Thr Ser Ser Trp Lys 3070 3075 3080	10246
	gaa aat gtg ata act tac agc tgc agg tct gga tat gtc ata caa Glu Asn Val Ile Thr Tyr Ser Cys Arg Ser Gly Tyr Val Ile Gln 3085 3090 3095	10291
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	gaa gtg aaa ctc aga tgt ctg gaa ggt tat acg atg gat aca gat Glu Val Lys Leu Arg Cys Leu Glu Gly Tyr Thr Met Asp Thr Asp 3145 3150 3155	10471
25	aca gat aca ttc acc tgt cag aaa gat ggt cgc tgg ttc cct gag Thr Asp Thr Phe Thr Cys Gln Lys Asp Gly Arg Trp Phe Pro Glu 3160 3165 3170	10516
	aga atc tcc tgc agt cct aaa aaa tgt cct ctc ccg gaa aac ata Arg Ile Ser Cys Ser Pro Lys Lys Cys Pro Leu Pro Glu Asn Ile 3175 3180 3185	10561
30	aca cat ata ctt gta cat ggg gac gat ttc agt gtg aat agg caa Thr His Ile Leu Val His Gly Asp Asp Phe Ser Val Asn Arg Gln 3190 3195 3200	10606
	gtt tct gtg tca tgt gca gaa ggg tat acc ttt gag gga gtt aac Val Ser Val Ser Cys Ala Glu Gly Tyr Thr Phe Glu Gly Val Asn 3205 3210 3215	10651
35	ata tca gta tgt cag ctt gat gga acc tgg gag cca cca ttc tcc Ile Ser Val Cys Gln Leu Asp Gly Thr Trp Glu Pro Pro Phe Ser 3220 3225 3230	10696
	gat gaa tct tgc agt cca gtt tct tgt ggg aaa cct gaa agt cca Asp Glu Ser Cys Ser Pro Val Ser Cys Gly Lys Pro Glu Ser Pro 3235 3240 3245	10741
40	gaa cat gga ttt gtg gtt ggc agt aaa tac acc ttt gaa agc aca Glu His Gly Phe Val Val Gly Ser Lys Tyr Thr Phe Glu Ser Thr 3250 3255 3260	10786

5	att att tat cag tgt gag cct ggc tat gaa cta gag ggg aac agg Ile Ile Tyr Gln Cys Glu Pro Gly Tyr Glu Leu Glu Gly Asn Arg 3265 3270 3275	10831
	gaa cgt gtc tgc cag gag aac aga cag tgg agt gga ggg gtg gca Glu Arg Val Cys Gln Glu Asn Arg Gln Trp Ser Gly Gly Val Ala	10876
10	3280 3285 3290	
	ata tgc aaa gag acc agg tgt gaa act cca ctt gaa ttt ctc aat Ile Cys Lys Glu Thr Arg Cys Glu Thr Pro Leu Glu Phe Leu Asn 3295 3300 3305	10921
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15	tat tcc tgc aac aga ggc tac agt ctt gaa ggg cca tct gag gca Tyr Ser Cys Asn Arg Gly Tyr Ser Leu Glu Gly Pro Ser Glu Ala 3325 3330 3335	11011
20	cac tgc aca gaa aat gga acc tgg agc cac cca gtc cct ctc tgc His Cys Thr Glu Asn Gly Thr Trp Ser His Pro Val Pro Leu Cys 3340 3345 3350	11056
	aaa cca aat cca tgc cct gtt cct ttt gtg att ccc gag aat gct Lys Pro Asn Pro Cys Pro Val Pro Phe Val Ile Pro Glu Asn Ala 3355 3360 3365	11101
25	ctg ctg tct gaa aag gag ttt tat gtt gat cag aat gtg tcc atc Leu Leu Ser Glu Lys Glu Phe Tyr Val Asp Gln Asn Val Ser Ile 3370 3375 3380	11146
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30	tgc aac ccc gac gag acg tgg aca cag aca agc gcc aaa tgt gaa Cys Asn Pro Asp Glu Thr Trp Thr Gln Thr Ser Ala Lys Cys Glu 3400 3405 3410	11236
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35	cga ggc gta cat tat caa tat gga gac atg atc acc tac tca tgt Arg Gly Val His Tyr Gln Tyr Gly Asp Met Ile Thr Tyr Ser Cys 3430 3435 3440	11326
	tac agt gga tac atg ttg gag ggt ttc ctg agg agt gtt tgt tta Tyr Ser Gly Tyr Met Leu Glu Gly Phe Leu Arg Ser Val Cys Leu 3445 3450 3455	11371
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	cga ttt cca tgt cag aat ggg ggc atc tgc caa cgc cca aat gct Arg Phe Pro Cys Gln Asn Gly Gly Ile Cys Gln Arg Pro Asn Ala 3475 3480 3485	11461

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	Cys Ser Cys Pro Glu Gly Trp Met	Gly Arg Leu Cys Glu	Glu Pro	
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	atc tgc att ctt ccc tgt ctg aac	gga ggt cgc tgt gtg	gcc cct	11551
	Ile Cys Ile Leu Pro Cys Leu Asn	Gly Gly Arg Cys Val	Ala Pro	
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	tac cag tgt gac tgc ccg cct ggc	tgg acg ggg tct cgc	tgt cat	11596
	Tyr Gln Cys Asp Cys Pro Pro Gly	Trp Thr Gly Ser Arg	Cys His	
	3520	3525	3530	
	aca gct gtt tgc cag tct ccc tgc	tta aat ggt gga aaa	tgt gta	11641
15	Thr Ala Val Cys Gln Ser Pro Cys	Leu Asn Gly Gly Lys	Cys Val	
	3535	3540	3545	
	aga cca aac cga tgt cac tgt ctt	tct tct tgg acg gga	cat aac	11686
	Arg Pro Asn Arg Cys His Cys Ile	Ser Ser Trp Thr Gly	His Asn	
	3550	3555	3560	
20	tgt tcc agg aaa agg agg act ggg	ttt taa ccactgcacg accatctggc		11736
	Cys Ser Arg Lys Arg Arg Thr Gly Phe			
	3565	3570		
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	agaaaagtcca acatggtgct gggcttttt tagtaaactt gttacttggg gttacttttt			11856
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	<212> PRT			
	<213> Homo sapiens			
	<400> 2			
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	Gly Trp Ala Thr Phe Gln Gln Met Ser Pro Ser Arg Asn Phe Ser Phe			
	20	25	30	
	Arg Leu Phe Pro Glu Thr Ala Pro Gly Ala Pro Gly Ser Ile Pro Ala			
	35	40	45	
40	Pro Pro Ala Pro Gly Asp Glu Ala Ala Gly Ser Arg Val Glu Arg Leu			
	50	55	60	
	Gly Gln Ala Phe Arg Arg Val Arg Leu Leu Arg Glu Leu Ser Glu			
	65	70	75	80
	Arg Leu Glu Leu Val Phe Leu Val Asp Asp Ser Ser Ser Val Gly Glu			
45	85	90	95	
	Val Asn Phe Arg Ser Glu Leu Met Phe Val Arg Lys Leu Leu Ser Asp			
	100	105	110	
	Phe Pro Val Val Pro Thr Ala Thr Arg Val Ala Ile Val Thr Phe Ser			
	115	120	125	

5 Ser Lys Asn Tyr Val Val Pro Arg Val Asp Tyr Ile Ser Thr Arg Arg
 130 - 135 140
 Ala Arg Gln His Lys Cys Ala Leu Leu Leu Gln Glu Ile Pro Ala Ile
 145 150 155 160
 Ser Tyr Arg Gly Gly Thr Tyr Thr Lys Gly Ala Phe Gln Gln Ala
 10 165 170 175
 Ala Gln Ile Leu Leu His Ala Arg Glu Asn Ser Thr Lys Val Val Phe
 180 185 190
 Leu Ile Thr Asp Gly Tyr Ser Asn Gly Gly Asp Pro Arg Pro Ile Ala
 195 200 205
 15 Ala Ser Leu Arg Asp Ser Gly Val Glu Ile Phe Thr Phe Gly Ile Trp
 210 215 220
 Gln Gly Asn Ile Arg Glu Leu Asn Asp Met Ala Ser Thr Pro Lys Glu
 225 230 235 240
 Glu His Cys Tyr Leu Leu His Ser Phe Glu Glu Phe Glu Ala Leu Ala
 20 245 250 255
 Arg Arg Ala Leu His Glu Asp Leu Pro Ser Gly Ser Phe Ile Gln Asp
 260 265 270
 Asp Met Val His Cys Ser Tyr Leu Cys Asp Glu Gly Lys Asp Cys Cys
 275 280 285
 25 Asp Arg Met Gly Ser Cys Lys Cys Gly Thr His Thr Gly His Phe Glu
 290 295 300
 Cys Ile Cys Glu Lys Gly Tyr Tyr Gly Lys Gly Leu Gln Tyr Glu Cys
 305 310 315 320
 Thr Ala Cys Pro Ser Gly Thr Tyr Lys Pro Glu Gly Ser Pro Gly Gly
 30 325 330 335
 Ile Ser Ser Cys Ile Pro Cys Pro Asp Glu Asn His Thr Ser Pro Pro
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 Gly Ser Thr Ser Pro Glu Asp Cys Val Cys Arg Glu Gly Tyr Arg Ala
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 35 Ser Gly Gln Thr Cys Glu Leu Val His Cys Pro Ala Leu Lys Pro Pro
 370 375 380
 Glu Asn Gly Tyr Phe Ile Gln Asn Thr Cys Asn Asn His Phe Asn Ala
 385 390 395 400
 Ala Cys Gly Val Arg Cys His Pro Gly Phe Asp Leu Val Gly Ser Ser
 40 405 410 415
 Ile Ile Leu Cys Leu Pro Asn Gly Leu Trp Ser Gly Ser Glu Ser Tyr
 420 425 430
 Cys Arg Val Arg Thr Cys Pro His Leu Arg Gln Pro Lys His Gly His
 435 440 445
 45 Ile Ser Cys Ser Thr Arg Glu Met Leu Tyr Lys Thr Thr Cys Leu Val
 450 455 460
 Ala Cys Asp Glu Gly Tyr Arg Leu Glu Gly Ser Asp Lys Leu Thr Cys
 465 470 475 480
 Gln Gly Asn Ser Gln Trp Asp Gly Pro Glu Pro Arg Cys Val Glu Arg

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	His Cys Ser Thr Phe Gln Met Pro Lys Asp Val Ile Ile Ser Pro His		
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	Asn Cys Gly Lys Gln Pro Ala Lys Phe Gly Thr Ile Cys Tyr Val Ser		
	515	520	525
10	Cys Arg Gln Gly Phe Ile Leu Ser Gly Val Lys Glu Met Leu Arg Cys		
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	Thr Thr Ser Gly Lys Trp Asn Val Gly Val Gln Ala Ala Val Cys Lys		
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	Asp Val Glu Ala Pro Gln Ile Asn Cys Pro Lys Asp Ile Glu Ala Lys		
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	Thr Leu Glu Gln Gln Asp Ser Ala Asn Val Thr Trp Gln Ile Pro Thr		
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	Ala Lys Asp Asn Ser Gly Glu Lys Val Ser Val His Val His Pro Ala		
	595	600	605
20	Phe Thr Pro Pro Tyr Leu Phe Pro Ile Gly Asp Val Ala Ile Val Tyr		
	610	615	620
	Thr Ala Thr Asp Leu Ser Gly Asn Gln Ala Ser Cys Ile Phe His Ile		
	625	630	635
	Lys Val Ile Asp Ala Glu Pro Pro Val Ile Asp Trp Cys Arg Ser Pro		
25	645	650	655
	Pro Pro Val Gln Val Ser Glu Lys Val His Ala Ala Ser Trp Asp Glu		
	660	665	670
	Pro Gln Phe Ser Asp Asn Ser Gly Ala Glu Leu Val Ile Thr Arg Ser		
	675	680	685
30	His Thr Gln Gly Asp Leu Phe Pro Gln Gly Glu Thr Ile Val Gln Tyr		
	690	695	700
	Thr Ala Thr Asp Pro Ser Gly Asn Asn Arg Thr Cys Asp Ile His Ile		
	705	710	715
	Val Ile Lys Gly Ser Pro Cys Glu Ile Pro Phe Thr Pro Val Asn Gly		
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	Asp Phe Ile Cys Thr Pro Asp Asn Thr Gly Val Asn Cys Thr Leu Thr		
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	Cys Leu Glu Gly Tyr Asp Phe Thr Glu Gly Ser Thr Asp Lys Tyr Tyr		
	755	760	765
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	770	775	780
	Pro Asp Cys Ala Lys Lys Arg Phe Ala Asn His Gly Phe Lys Ser Phe		
	785	790	795
	Glu Met Phe Tyr Lys Ala Ala Arg Cys Asp Asp Thr Asp Leu Met Lys		
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	Lys Phe Ser Glu Ala Phe Glu Thr Thr Leu Gly Lys Met Val Pro Ser		
	820	825	830
	Phe Cys Ser Asp Ala Glu Asp Ile Asp Cys Arg Leu Glu Glu Asn Leu		
	835	840	845

5 Thr Lys Lys Tyr Cys Leu Glu Tyr Asn Tyr Asp Tyr Glu Asn Gly Phe
 850 - 855 860
 Ala Ile Gly Pro Gly Gly Trp Gly Ala Ala Asn Arg Leu Asp Tyr Ser
 865 870 875 880
 Tyr Asp Asp Phe Leu Asp Thr Val Gln Glu Thr Ala Thr Ser Ile Gly
 10 885 890 895
 Asn Ala Lys Ser Ser Arg Ile Lys Arg Ser Ala Pro Leu Ser Asp Tyr
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 Lys Ile Lys Leu Ile Phe Asn Ile Thr Ala Ser Val Pro Leu Pro Asp
 915 920 925
 15 Glu Arg Asn Asp Thr Leu Glu Trp Glu Asn Gln Gln Arg Leu Leu Gln
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 Thr Leu Glu Thr Ile Thr Asn Lys Leu Lys Arg Thr Leu Asn Lys Asp
 945 950 955 960
 Pro Met Tyr Ser Phe Gln Leu Ala Ser Glu Ile Leu Ile Ala Asp Ser
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 Asn Ser Leu Glu Thr Lys Lys Ala Ser Pro Phe Cys Arg Pro Gly Ser
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 Val Leu Arg Gly Arg Met Cys Val Asn Cys Pro Leu Gly Thr Tyr Tyr
 995 1000 1005
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 Ile Ser Ser Gln Val Phe His Glu Cys Phe Phe Asn Pro Cys His

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	Cys Pro	Leu Gly Tyr Thr Gly	Leu Lys Cys Glu Thr Asp Ile Asp
	1220	1225	1230
10	Glu Cys	Ser Pro Leu Pro Cys	Leu Asn Asn Gly Val Cys Lys Asp
	1235	1240	1245
	Leu Val	Gly Glu Phe Ile Cys	Glu Cys Pro Ser Gly Tyr Thr Gly
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	Gln Arg	Cys Glu Glu Asn Ile	Asn Glu Cys Ser Ser Pro Cys
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	Leu Asn	Lys Gly Ile Cys Val	Asp Gly Val Ala Gly Tyr Arg Cys
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	Thr Cys	Val Lys Gly Phe Val	Gly Leu His Cys Glu Thr Glu Val
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	1310	1315	1320
	Asp Gln	Val Gly Gly Phe Leu	Cys Lys Cys Pro Pro Gly Phe Leu
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	Gly Thr	Arg Cys Gly Lys Asn	Val Asp Glu Cys Leu Ser Gln Pro
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	Cys Lys	Asn Gly Ala Thr Cys	Lys Asp Gly Ala Asn Ser Phe Arg
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	Cys Leu	Cys Ala Ala Gly Phe	Thr Gly Ser His Cys Glu Leu Asn
	1370	1375	1380
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	1385	1390	1395
	Val Asp	Glu Leu Asn Ser Tyr	Ser Cys Lys Cys Gln Pro Gly Phe
	1400	1405	1410
	Ser Gly	Lys Arg Cys Glu Thr	Glu Gln Ser Thr Gly Phe Asn Leu
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	Asp Phe	Glu Val Ser Gly Ile	Tyr Gly Tyr Val Met Leu Asp Gly
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	Met Leu	Pro Ser Leu His Ala	Leu Thr Cys Thr Phe Trp Met Lys
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	Asp Asn	Gly Ser Asp Asn Thr	Leu Leu Leu Thr Asp Tyr Asn Gly
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	Trp Val	Leu Tyr Val Asn Gly	Arg Glu Lys Ile Thr Asn Cys Pro
45	1490	1495	1500
	Ser Val	Asn Asp Gly Arg Trp	His His Ile Ala Ile Thr Trp Thr
	1505	1510	1515
	Ser Ala	Asn Gly Ile Trp Lys	Val Tyr Ile Asp Gly Lys Leu Ser
	1520	1525	1530

5 Asp Gly Gly Ala Gly Leu Ser Val Gly Leu Pro Ile Pro Gly Gly
 1535- 1540 1545
 Gly Ala Leu Val Leu Gly Gln Glu Gln Asp Lys Lys Gly Glu Gly
 1550 1555 1560
 Phe Ser Pro Ala Glu Ser Phe Val Gly Ser Ile Ser Gln Leu Asn
 10 1565 1570 1575
 Leu Trp Asp Tyr Val Leu Ser Pro Gln Gln Val Lys Ser Leu Ala
 1580 1585 1590
 Thr Ser Cys Pro Glu Glu Leu Ser Lys Gly Asn Val Leu Ala Trp
 1595 1600 1605
 15 Pro Asp Phe Leu Ser Gly Ile Val Gly Lys Val Lys Ile Asp Ser
 1610 1615 1620
 Lys Ser Ile Phe Cys Ser Asp Cys Pro Arg Leu Gly Gly Ser Val
 1625 1630 1635
 Pro His Leu Arg Thr Ala Ser Glu Asp Leu Lys Pro Gly Ser Lys
 20 1640 1645 1650
 Val Asn Leu Phe Cys Asp Pro Gly Phe Gln Leu Val Gly Asn Pro
 1655 1660 1665
 Val Gln Tyr Cys Leu Asn Gln Gly Gln Trp Thr Gln Pro Leu Pro
 1670 1675 1680
 25 His Cys Glu Arg Ile Ser Cys Gly Val Pro Pro Pro Leu Glu Asn
 1685 1690 1695
 Gly Phe His Ser Ala Asp Asp Phe Tyr Ala Gly Ser Thr Val Thr
 1700 1705 1710
 Tyr Gln Cys Asn Asn Gly Tyr Tyr Leu Leu Gly Asp Ser Arg Met
 30 1715 1720 1725
 Phe Cys Thr Asp Asn Gly Ser Trp Asn Gly Val Ser Pro Ser Cys
 1730 1735 1740
 Leu Asp Val Asp Glu Cys Ala Val Gly Ser Asp Cys Ser Glu His
 1745 1750 1755
 35 Ala Ser Cys Leu Asn Val Asp Gly Ser Tyr Ile Cys Ser Cys Val
 1760 1765 1770
 Pro Pro Tyr Thr Gly Asp Gly Lys Asn Cys Ala Glu Pro Ile Lys
 1775 1780 1785
 Cys Lys Ala Pro Gly Asn Pro Glu Asn Gly His Ser Ser Gly Glu
 40 1790 1795 1800
 Ile Tyr Thr Val Gly Ala Ala Val Thr Phe Ser Cys Gln Glu Gly
 1805 1810 1815
 Tyr Gln Leu Met Gly Val Thr Lys Ile Thr Cys Leu Glu Ser Gly
 1820 1825 1830
 45 Glu Trp Asn His Leu Ile Pro Tyr Cys Lys Ala Val Ser Cys Gly
 1835 1840 1845
 Lys Pro Ala Ile Pro Glu Asn Gly Cys Ile Glu Glu Leu Ala Phe
 1850 1855 1860
 Thr Phe Gly Ser Lys Val Thr Tyr Arg Cys Asn Lys Gly Tyr Thr

5	1865	1870	1875	
	Leu Ala	Gly Asp Lys Glu Ser	Ser Cys Leu Ala Asn	Ser Ser Trp
	1880	1885	1890	
	Ser His	Ser Pro Pro Val	Cys Glu Pro Val Lys	Cys Ser Ser Pro
	1895	1900	1905	
10	Glu Asn Ile Asn Asn Gly Lys	Tyr Ile Leu Ser Gly	Leu Thr Tyr	
	1910	1915	1920	
	Leu Ser Thr Ala Ser Tyr Ser	Cys Asp Thr Gly Tyr	Ser Leu Gln	
	1925	1930	1935	
	Gly Pro Ser Ile Ile Glu Cys	Thr Ala Ser Gly Ile	Trp Asp Arg	
15	1940	1945	1950	
	Ala Pro Pro Ala Cys His Leu	Val Phe Cys Gly Glu	Pro Pro Ala	
	1955	1960	1965	
	Ile Lys Asp Ala Val Ile Thr	Gly Asn Asn Phe Thr	Phe Arg Asn	
	1970	1975	1980	
20	Thr Val Thr Tyr Thr Cys Lys	Glu Gly Tyr Thr Leu	Ala Gly Leu	
	1985	1990	1995	
	Asp Thr Ile Glu Cys Leu Ala	Asp Gly Lys Trp Ser	Arg Ser Asp	
	2000	2005	2010	
	Gln Gln Cys Leu Ala Val Ser	Cys Asp Glu Pro Pro	Ile Val Asp	
25	2015	2020	2025	
	His Ala Ser Pro Glu Thr Ala	His Arg Leu Phe Gly	Asp Ile Ala	
	2030	2035	2040	
	Phe Tyr Tyr Cys Ser Asp Gly	Tyr Ser Leu Ala Asp	Asn Ser Gln	
	2045	2050	2055	
30	Leu Leu Cys Asn Ala Gln Gly	Lys Trp Val Pro Pro	Glu Gly Gln	
	2060	2065	2070	
	Asp Met Pro Arg Cys Ile Ala	His Phe Cys Glu Lys	Pro Pro Ser	
	2075	2080	2085	
	Val Ser Tyr Ser Ile Leu Glu	Ser Val Ser Lys Ala	Lys Phe Ala	
35	2090	2095	2100	
	Ala Gly Ser Val Val Ser Phe.	Lys Cys Met Glu Gly	Phe Val Leu	
	2105	2110	2115	
	Asn Thr Ser Ala Lys Ile Glu	Cys Met Arg Gly	Gly Gln Trp Asn	
	2120	2125	2130	
40	Pro Ser Pro Met Ser Ile Gln	Cys Ile Pro Val Arg	Cys Gly Glu	
	2135	2140	2145	
	Pro Pro Ser Ile Met Asn Gly	Tyr Ala Ser Gly Ser	Asn Tyr Ser	
	2150	2155	2160	
	Phe Gly Ala Met Val Ala Tyr	Ser Cys Asn Lys Gly	Phe Tyr Ile	
45	2165	2170	2175	
	Lys Gly Glu Lys Lys Ser Thr	Cys Glu Ala Thr Gly	Gln Trp Ser	
	2180	2185	2190	
	Ser Pro Ile Pro Thr Cys His	Pro Val Ser Cys Gly	Glu Pro Pro	
	2195	2200	2205	

5 Lys Val Glu Asn Gly Phe Leu Glu His Thr Thr Gly Arg Ile Phe
 2210 2215 2220
 Glu Ser Glu Val Arg Tyr Gln Cys Asn Pro Gly Tyr Lys Ser Val
 2225 2230 2235
 Gly Ser Pro Val Phe Val Cys Gln Ala Asn Arg His Trp His Ser
 10 2240 2245 2250
 Glu Ser Pro Leu Met Cys Val Pro Leu Asp Cys Gly Lys Pro Pro
 2255 2260 2265
 Pro Ile Gln Asn Gly Phe Met Lys Gly Glu Asn Phe Glu Val Gly
 2270 2275 2280
 15 Ser Lys Val Gln Phe Phe Cys Asn Glu Gly Tyr Glu Leu Val Gly
 2285 2290 2295
 Asp Ser Ser Trp Thr Cys Gln Lys Ser Gly Lys Trp Asn Lys Lys
 2300 2305 2310
 Ser Asn Pro Lys Cys Met Pro Ala Lys Cys Pro Glu Pro Pro Leu
 20 2315 2320 2325
 Leu Glu Asn Gln Leu Val Leu Lys Glu Leu Thr Thr Glu Val Gly
 2330 2335 2340
 Val Val Thr Phe Ser Cys Lys Glu Gly His Val Leu Gln Gly Pro
 2345 2350 2355
 25 Ser Val Leu Lys Cys Leu Pro Ser Gln Gln Trp Asn Asp Ser Phe
 2360 2365 2370
 Pro Val Cys Lys Ile Val Leu Cys Thr Pro Pro Pro Leu Ile Ser
 2375 2380 2385
 Phe Gly Val Pro Ile Pro Ser Ser Ala Leu His Phe Gly Ser Thr
 30 2390 2395 2400
 Val Lys Tyr Ser Cys Val Gly Gly Phe Phe Leu Arg Gly Asn Ser
 2405 2410 2415
 Thr Thr Leu Cys Gln Pro Asp Gly Thr Trp Ser Ser Pro Leu Pro
 2420 2425 2430
 35 Glu Cys Val Pro Val Glu Cys Pro Gln Pro Glu Glu Ile Pro Asn
 2435 2440 2445
 Gly Ile Ile Asp Val Gln Gly Leu Ala Tyr Leu Ser Thr Ala Leu
 2450 2455 2460
 Tyr Thr Cys Lys Pro Gly Phe Glu Leu Val Gly Asn Thr Thr Thr
 40 2465 2470 2475
 Leu Cys Gly Glu Asn Gly His Trp Leu Gly Gly Lys Pro Thr Cys
 2480 2485 2490
 Lys Ala Ile Glu Cys Leu Lys Pro Lys Glu Ile Leu Asn Gly Lys
 2495 2500 2505
 45 Phe Ser Tyr Thr Asp Leu His Tyr Gly Gln Thr Val Thr Tyr Ser
 2510 2515 2520
 Cys Asn Arg Gly Phe Arg Leu Glu Gly Pro Ser Ala Leu Thr Cys
 2525 2530 2535
 Leu Glu Thr Gly Asp Trp Asp Val Asp Ala Pro Ser Cys Asn Ala

5	2540	2545	2550
	Ile His Cys Asp Ser Pro Gln	Pro Ile Glu Asn Gly	Phe Val Glu
	2555	2560	2565
	Gly Ala Asp Tyr Ser Tyr Gly	Ala Ile Ile Ile Tyr	Ser Cys Phe
	2570	2575	2580
10	Pro Gly Phe Gln Val Ala Gly	His Ala Met Gln Thr	Cys Glu Glu
	2585	2590	2595
	Ser Gly Trp Ser Ser Ser Ile	Pro Thr Cys Met Pro	Ile Asp Cys
	2600	2605	2610
	Gly Leu Pro Pro His Ile Asp	Phe Gly Asp Cys Thr	Lys Leu Lys
15	2615	2620	2625
	Asp Asp Gln Gly Tyr Phe Glu	Gln Glu Asp Asp Met	Met Glu Val
	2630	2635	2640
	Pro Tyr Val Thr Pro His Pro	Pro Tyr His Leu Gly	Ala Val Ala
	2645	2650	2655
20	Lys Thr Trp Glu Asn Thr Lys	Glu Ser Pro Ala Thr	His Ser Ser
	2660	2665	2670
	Asn Phe Leu Tyr Gly Thr Met	Val Ser Tyr Thr Cys	Asn Pro Gly
	2675	2680	2685
	Tyr Glu Leu Leu Gly Asn Pro	Val Leu Ile Cys Gln	Glu Asp Gly
25	2690	2695	2700
	Thr Trp Asn Gly Ser Ala Pro	Ser Cys Ile Ser Ile	Glu Cys Asp
	2705	2710	2715
	Leu Pro Thr Ala Pro Glu Asn	Gly Phe Leu Arg Phe	Thr Glu Thr
	2720	2725	2730
30	Ser Met Gly Ser Ala Val Gln	Tyr Ser Cys Lys Pro	Gly His Ile
	2735	2740	2745
	Leu Ala Gly Ser Asp Leu Arg	Leu Cys Leu Glu Asn	Arg Lys Trp
	2750	2755	2760
	Ser Gly Ala Ser Pro Arg Cys	Glu Ala Ile Ser Cys	Lys Lys Pro
35	2765	2770	2775
	Asn Pro Val Met Asn Gly Ser	Ile Lys Gly Ser Asn	Tyr Thr Tyr
	2780	2785	2790
	Leu Ser Thr Leu Tyr Tyr Glu	Cys Asp Pro Gly Tyr	Val Leu Asn
	2795	2800	2805
40	Gly Thr Glu Arg Arg Thr Cys	Gln Asp Asp Lys Asn	Trp Asp Glu
	2810	2815	2820
	Asp Glu Pro Ile Cys Ile Pro	Val Asp Cys Ser Ser	Pro Pro Val
	2825	2830	2835
	Ser Ala Asn Gly Gln Val Arg	Gly Asp Glu Tyr Thr	Phe Gln Lys
45	2840	2845	2850
	Glu Ile Glu Tyr Thr Cys Asn	Glu Gly Phe Leu Leu	Glu Gly Ala
	2855	2860	2865
	Arg Ser Arg Val Cys Leu Ala	Asn Gly Ser Trp Ser	Gly Ala Thr
	2870	2875	2880

5 Pro Asp Cys Val Pro Val Arg Cys Ala Thr Pro Pro Gln Leu Ala
 2885- 2890 2895
 Asn Gly Val Thr Glu Gly Leu Asp Tyr Gly Phe Met Lys Glu Val
 2900 2905 2910
 Thr Phe His Cys His Glu Gly Tyr Ile Leu His Gly Ala Pro Lys
 10 2915 2920 2925
 Leu Thr Cys Gln Ser Asp Gly Asn Trp Asp Ala Glu Ile Pro Leu
 2930 2935 2940
 Cys Lys Pro Val Asn Cys Gly Pro Pro Glu Asp Leu Ala His Gly
 2945 2950 2955
 15 Phe Pro Asn Gly Phe Ser Phe Ile His Gly Gly His Ile Gln Tyr
 2960 2965 2970
 Gln Cys Phe Pro Gly Tyr Lys Leu His Gly Asn Ser Ser Arg Arg
 2975 2980 2985
 Cys Leu Ser Asn Gly Ser Trp Ser Gly Ser Ser Pro Ser Cys Leu
 20 2990 2995 3000
 Pro Cys Arg Cys Ser Thr Pro Val Ile Glu Tyr Gly Thr Val Asn
 3005 3010 3015
 Gly Thr Asp Phe Asp Cys Gly Lys Ala Ala Arg Ile Gln Cys Phe
 3020 3025 3030
 25 Lys Gly Phe Lys Leu Leu Gly Leu Ser Glu Ile Thr Cys Glu Ala
 3035 3040 3045
 Asp Gly Gln Trp Ser Ser Gly Phe Pro His Cys Glu His Thr Ser
 3050 3055 3060
 Cys Gly Ser Leu Pro Met Ile Pro Asn Ala Phe Ile Ser Glu Thr
 30 3065 3070 3075
 Ser Ser Trp Lys Glu Asn Val Ile Thr Tyr Ser Cys Arg Ser Gly
 3080 3085 3090
 Tyr Val Ile Gln Gly Ser Ser Asp Leu Ile Cys Thr Glu Lys Gly
 3095 3100 3105
 35 Val Trp Ser Gln Pro Tyr Pro Val Cys Glu Pro Leu Ser Cys Gly
 3110 3115 3120
 Ser Pro Pro Ser Val Ala Asn Ala Val Ala Thr Gly Glu Ala His
 3125 3130 3135
 Thr Tyr Glu Ser Glu Val Lys Leu Arg Cys Leu Glu Gly Tyr Thr
 40 3140 3145 3150
 Met Asp Thr Asp Thr Asp Thr Phe Thr Cys Gln Lys Asp Gly Arg
 3155 3160 3165
 Trp Phe Pro Glu Arg Ile Ser Cys Ser Pro Lys Lys Cys Pro Leu
 3170 3175 3180
 45 Pro Glu Asn Ile Thr His Ile Leu Val His Gly Asp Asp Phe Ser
 3185 3190 3195
 Val Asn Arg Gln Val Ser Val Ser Cys Ala Glu Gly Tyr Thr Phe
 3200 3205 3210
 Glu Gly Val Asn Ile Ser Val Cys Gln Leu Asp Gly Thr Trp Glu

5	3215	3220	3225
	Pro Pro Phe Ser Asp Glu Ser Cys Ser Pro Val Ser Cys Gly Lys		
	3230	3235	3240
	Pro Glu Ser Pro Glu His Gly Phe Val Val Gly Ser Lys Tyr Thr		
	3245	3250	3255
10	Phe Glu Ser Thr Ile Ile Tyr Gln Cys Glu Pro Gly Tyr Glu Leu		
	3260	3265	3270
	Glu Gly Asn Arg Glu Arg Val Cys Gln Glu Asn Arg Gln Trp Ser		
	3275	3280	3285
	Gly Gly Val Ala Ile Cys Lys Glu Thr Arg Cys Glu Thr Pro Leu		
15	3290	3295	3300
	Glu Phe Leu Asn Gly Lys Ala Asp Ile Glu Asn Arg Thr Thr Gly		
	3305	3310	3315
	Pro Asn Val Val Tyr Ser Cys Asn Arg Gly Tyr Ser Leu Glu Gly		
	3320	3325	3330
20	Pro Ser Glu Ala His Cys Thr Glu Asn Gly Thr Trp Ser His Pro		
	3335	3340	3345
	Val Pro Leu Cys Lys Pro Asn Pro Cys Pro Val Pro Phe Val Ile		
	3350	3355	3360
	Pro Glu Asn Ala Leu Leu Ser Glu Lys Glu Phe Tyr Val Asp Gln		
25	3365	3370	3375
	Asn Val Ser Ile Lys Cys Arg Glu Gly Phe Leu Leu Gln Gly His		
	3380	3385	3390
	Gly Ile Ile Thr Cys Asn Pro Asp Glu Thr Trp Thr Gln Thr Ser		
	3395	3400	3405
30	Ala Lys Cys Glu Lys Ile Ser Cys Gly Pro Pro Ala His Val Glu		
	3410	3415	3420
	Asn Ala Ile Ala Arg Gly Val His Tyr Gln Tyr Gly Asp Met Ile		
	3425	3430	3435
	Thr Tyr Ser Cys Tyr Ser Gly Tyr Met Leu Glu Gly Phe Leu Arg		
35	3440	3445	3450
	Ser Val Cys Leu Glu Asn Gly Thr Trp Thr Ser Pro Pro Ile Cys		
	3455	3460	3465
	Arg Ala Val Cys Arg Phe Pro Cys Gln Asn Gly Gly Ile Cys Gln		
	3470	3475	3480
40	Arg Pro Asn Ala Cys Ser Cys Pro Glu Gly Trp Met Gly Arg Leu		
	3485	3490	3495
	Cys Glu Glu Pro Ile Cys Ile Leu Pro Cys Leu Asn Gly Gly Arg		
	3500	3505	3510
	Cys Val Ala Pro Tyr Gln Cys Asp Cys Pro Pro Gly Trp Thr Gly		
45	3515	3520	3525
	Ser Arg Cys His Thr Ala Val Cys Gln Ser Pro Cys Leu Asn Gly		
	3530	3535	3540
	Gly Lys Cys Val Arg Pro Asn Arg Cys His Cys Leu Ser Ser Trp		
	3545	3550	3555

5 Thr Gly His Asn Cys Ser Arg Lys Arg Arg Thr Gly Phe
3560 3565 3570

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